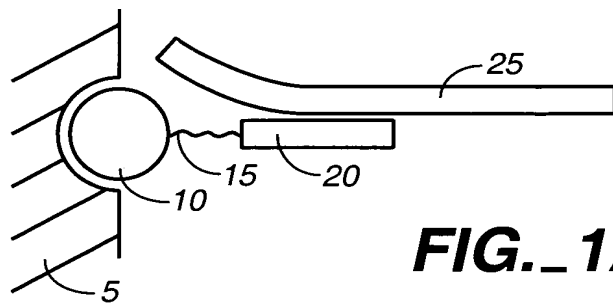


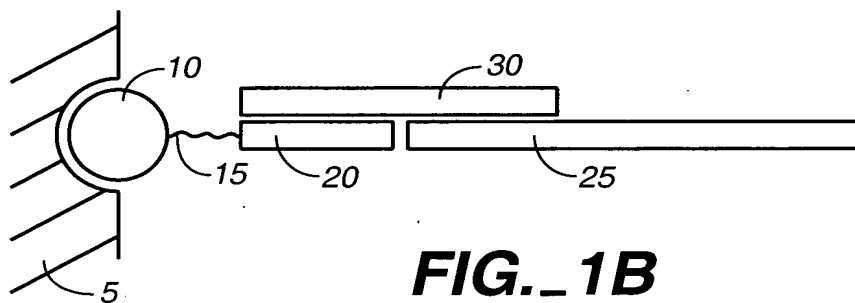
Please enter the following substitute drawings and consider the remarks herein.

**IN THE DRAWINGS**

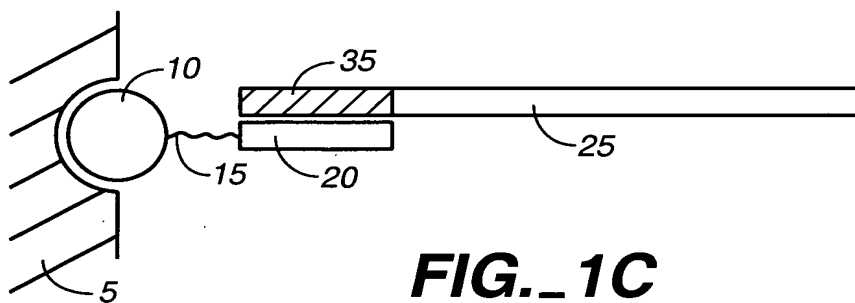
Please replace the original drawings as filed with the substitute drawings submitted herein.



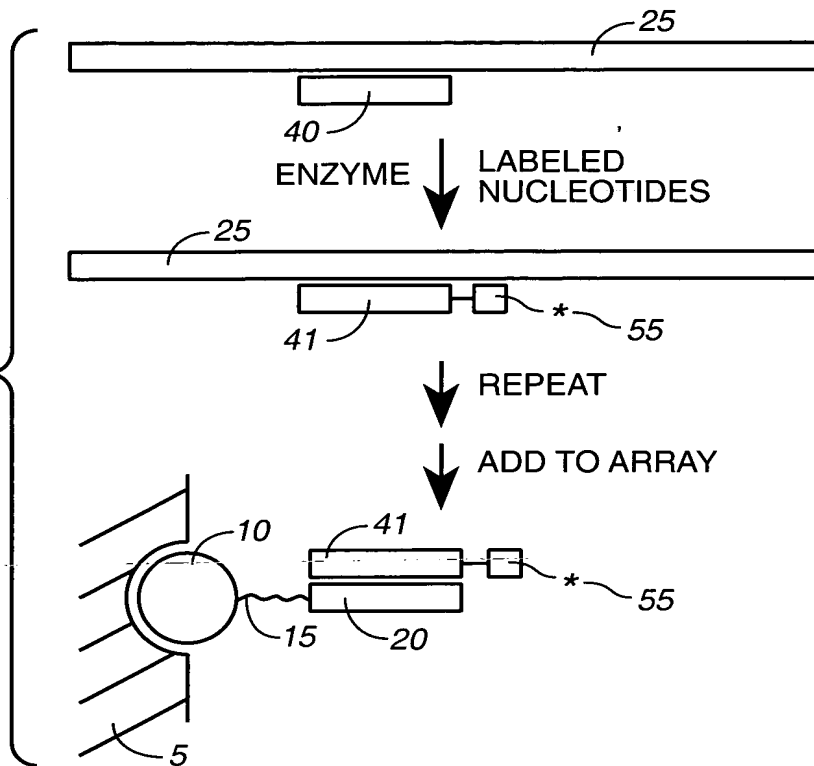
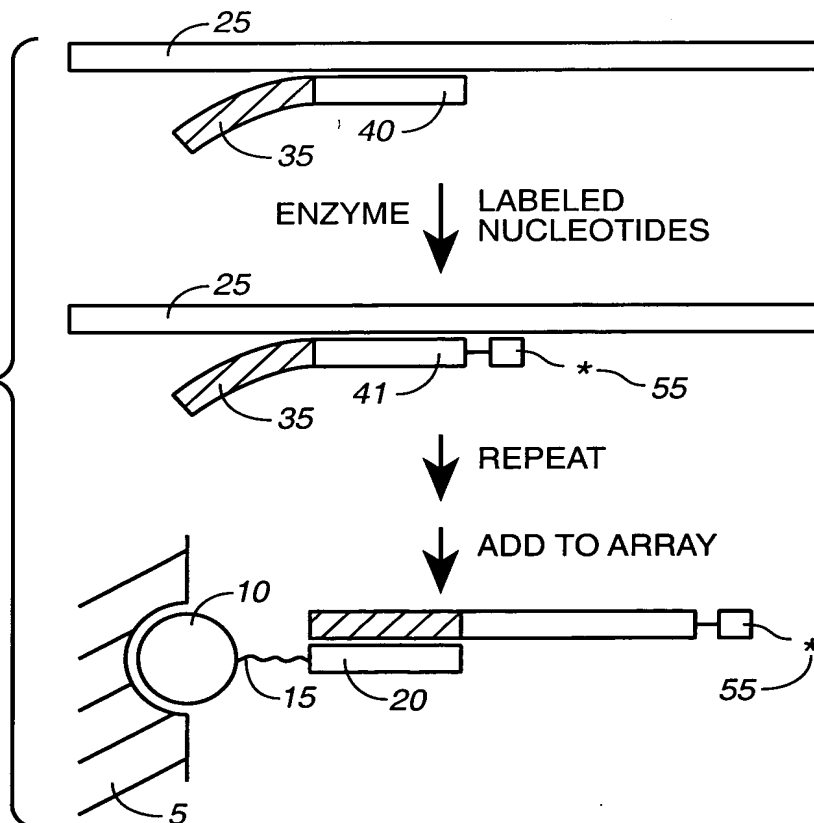
**FIG.\_1A**

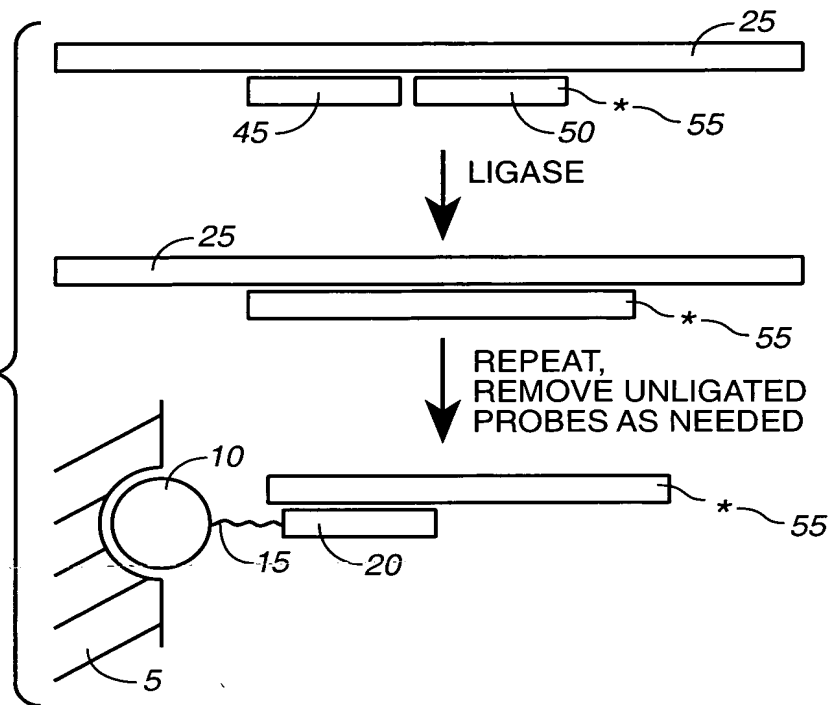
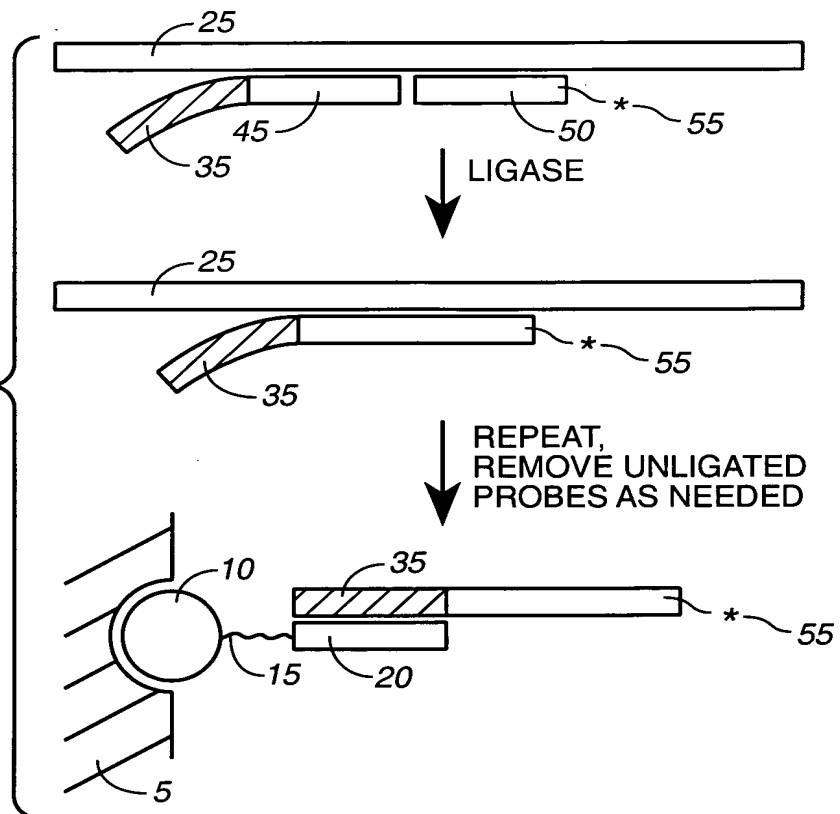


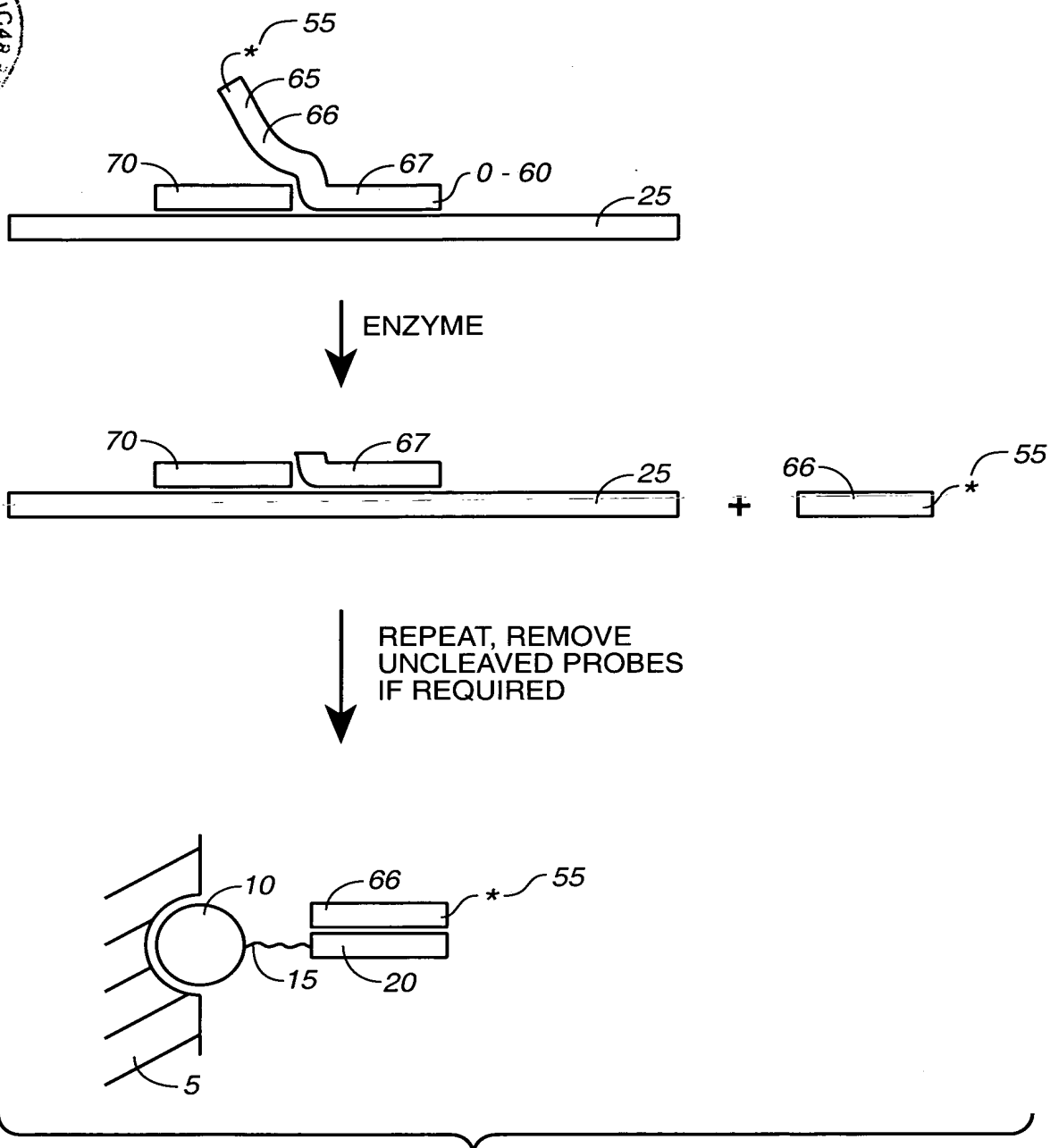
**FIG.\_1B**



**FIG.\_1C**

**FIG.\_2A****FIG.\_2B**

**FIG.\_3A****FIG.\_3B**

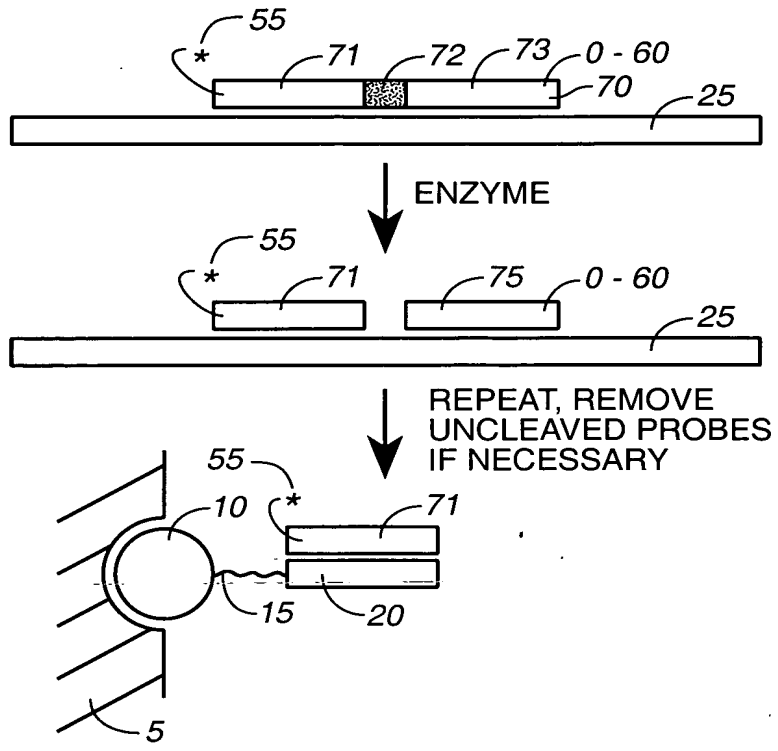


**FIG. 4**

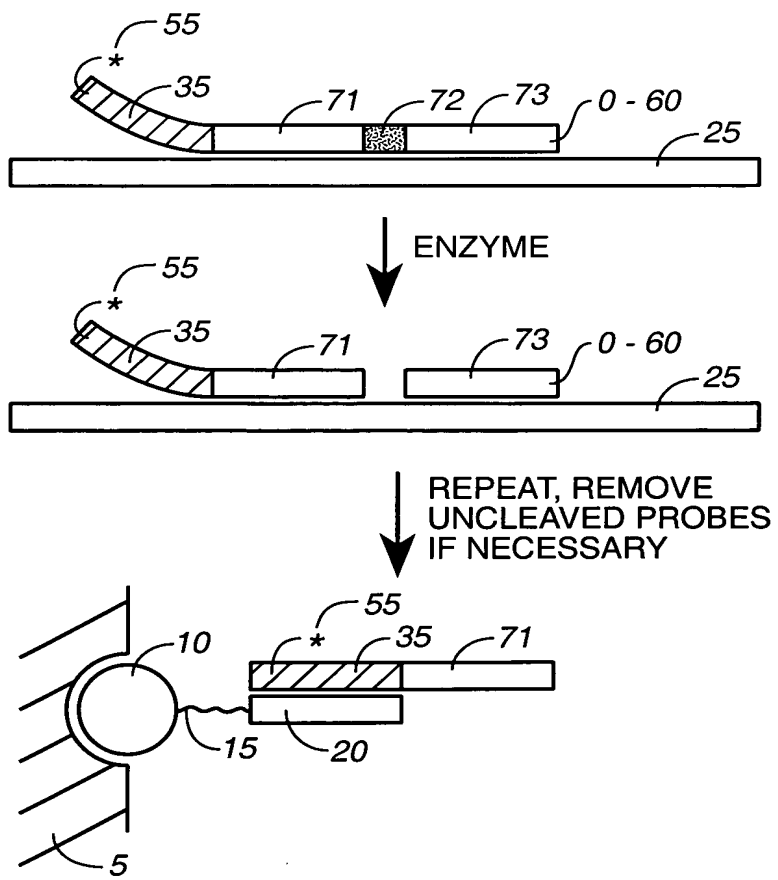
5 / 36

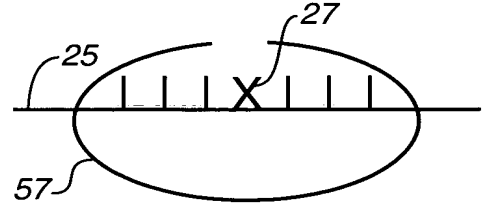
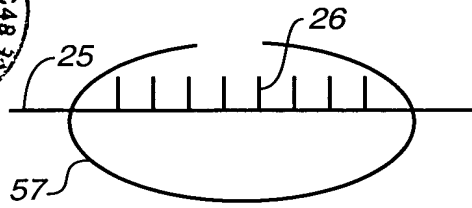


**FIG.\_5A**

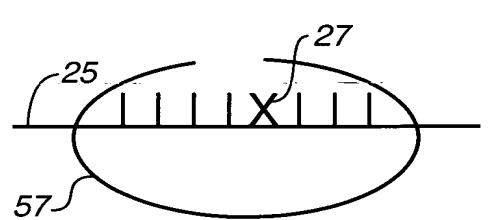
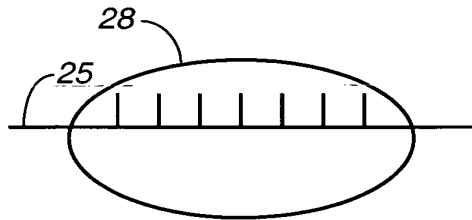


**FIG.\_5B**

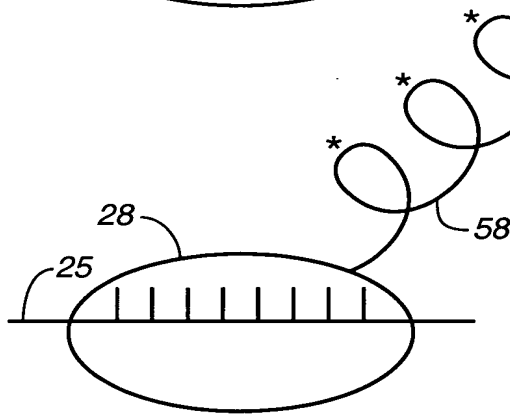
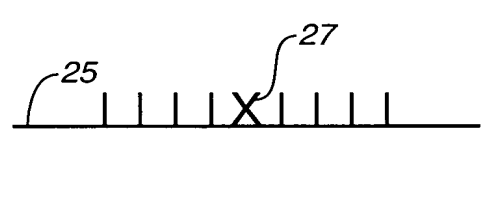
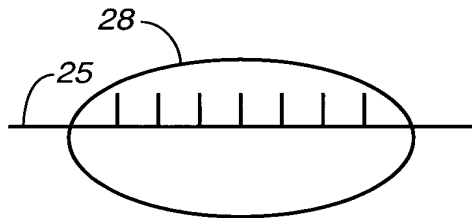




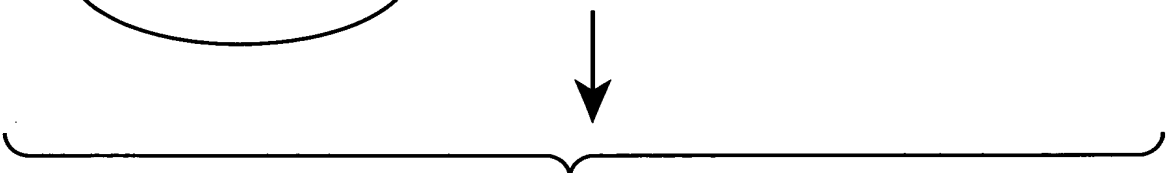
LIGASE



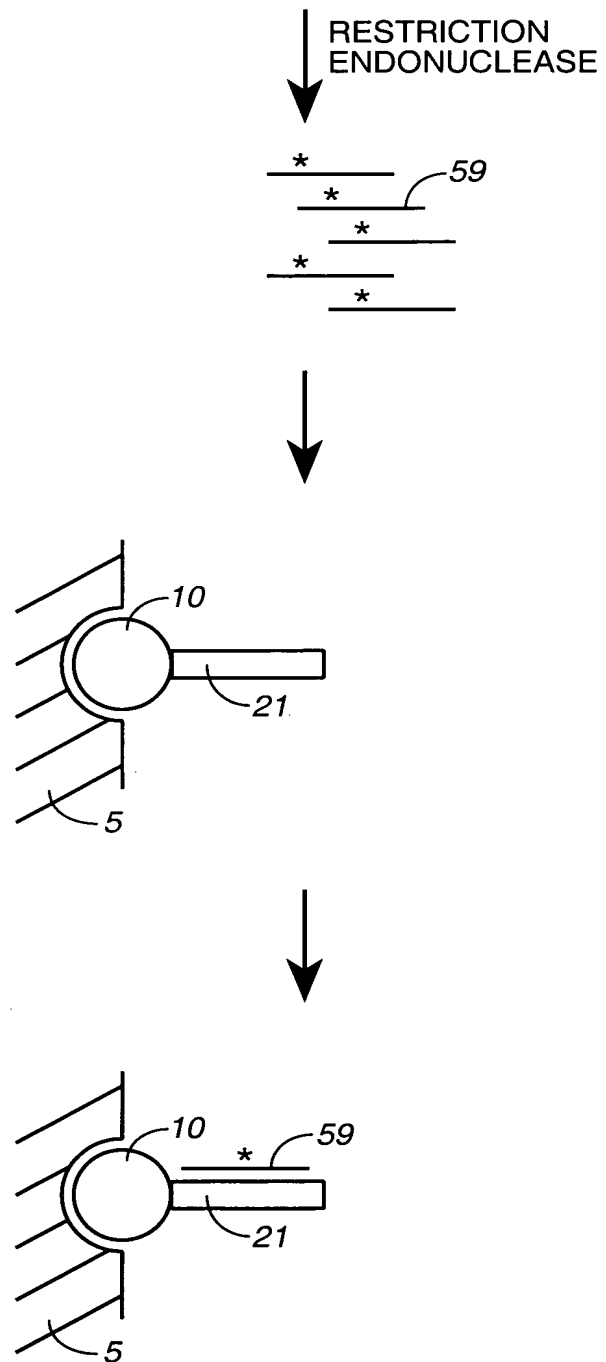
WASH



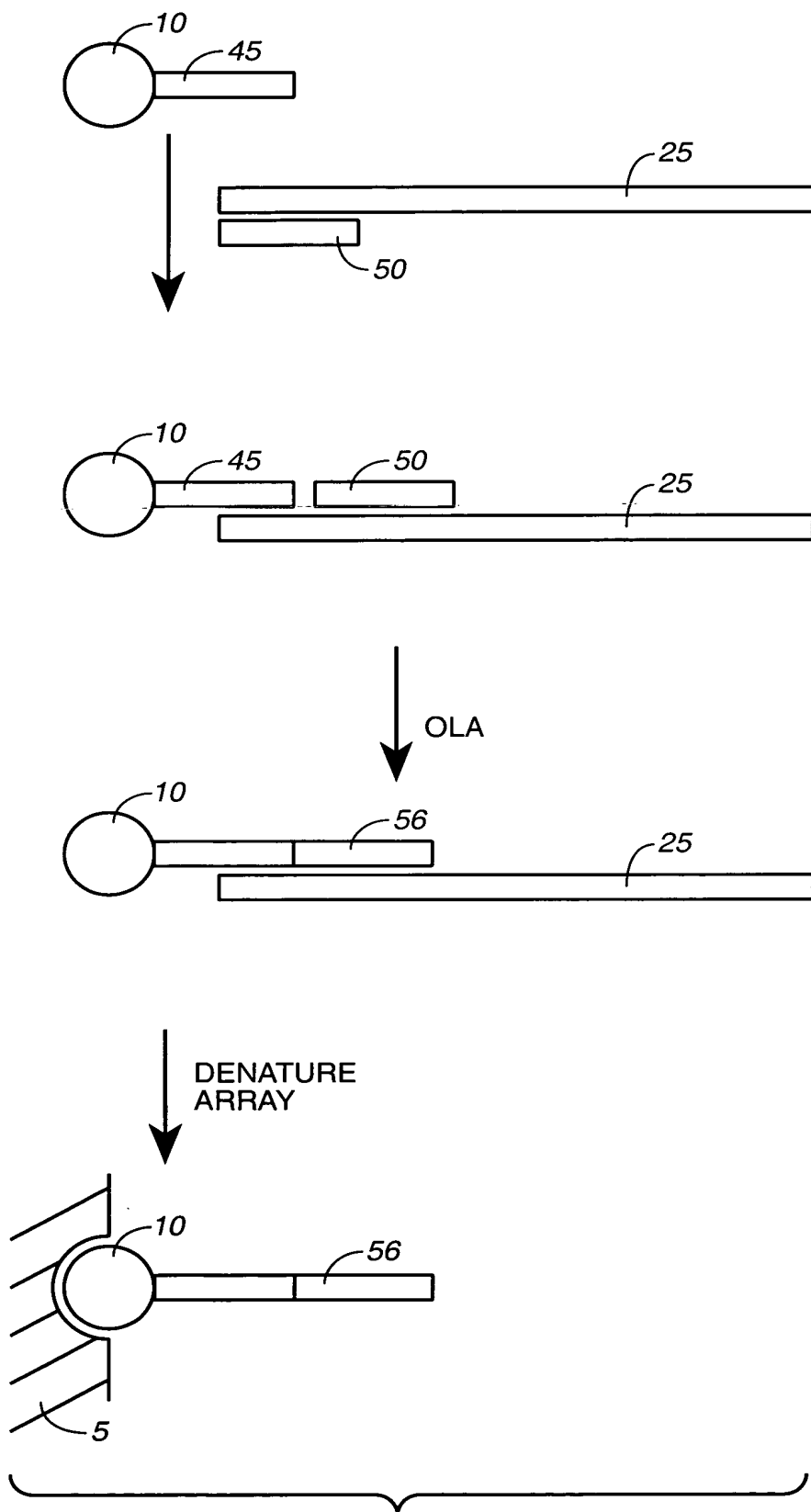
POLYMERASE  
NTPS\*

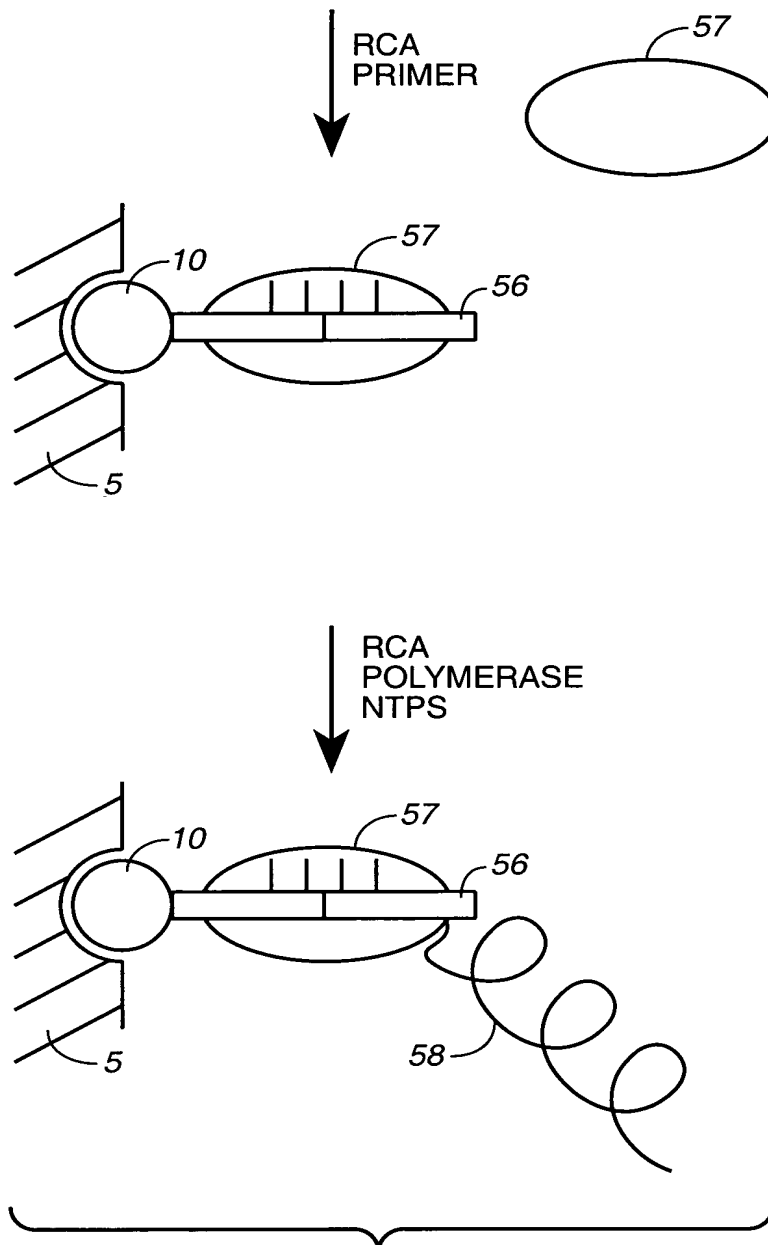


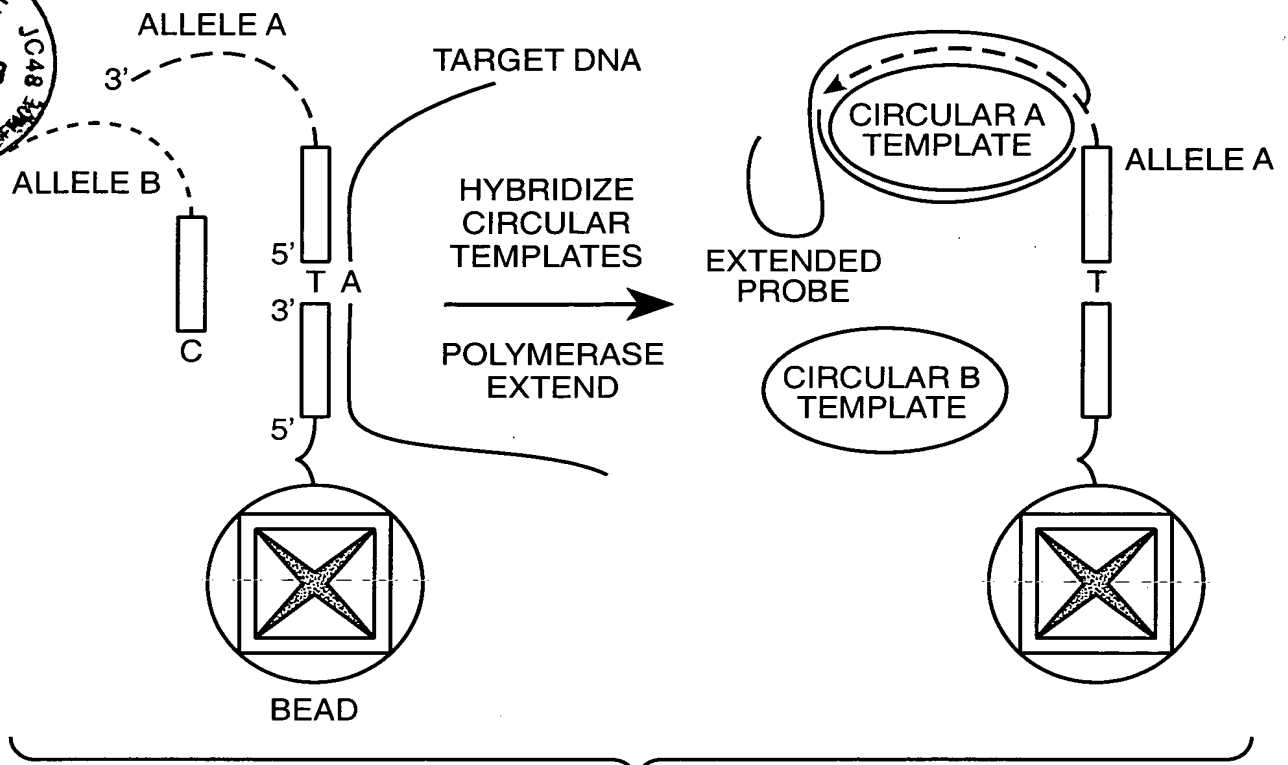
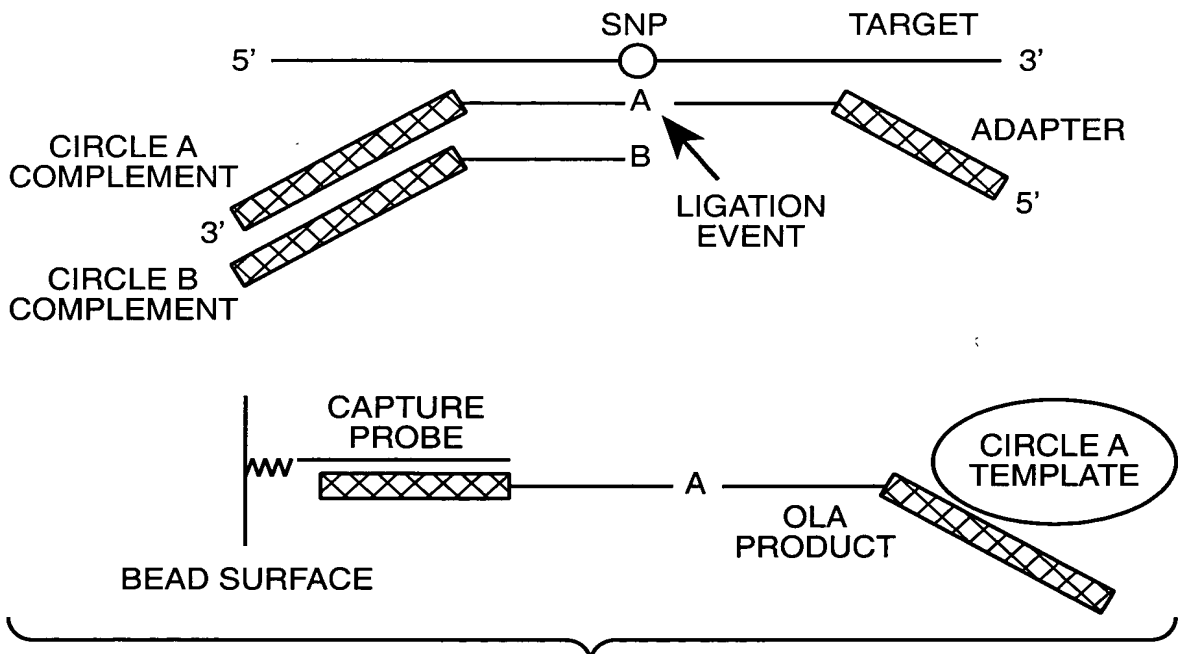
**FIG. 6A**

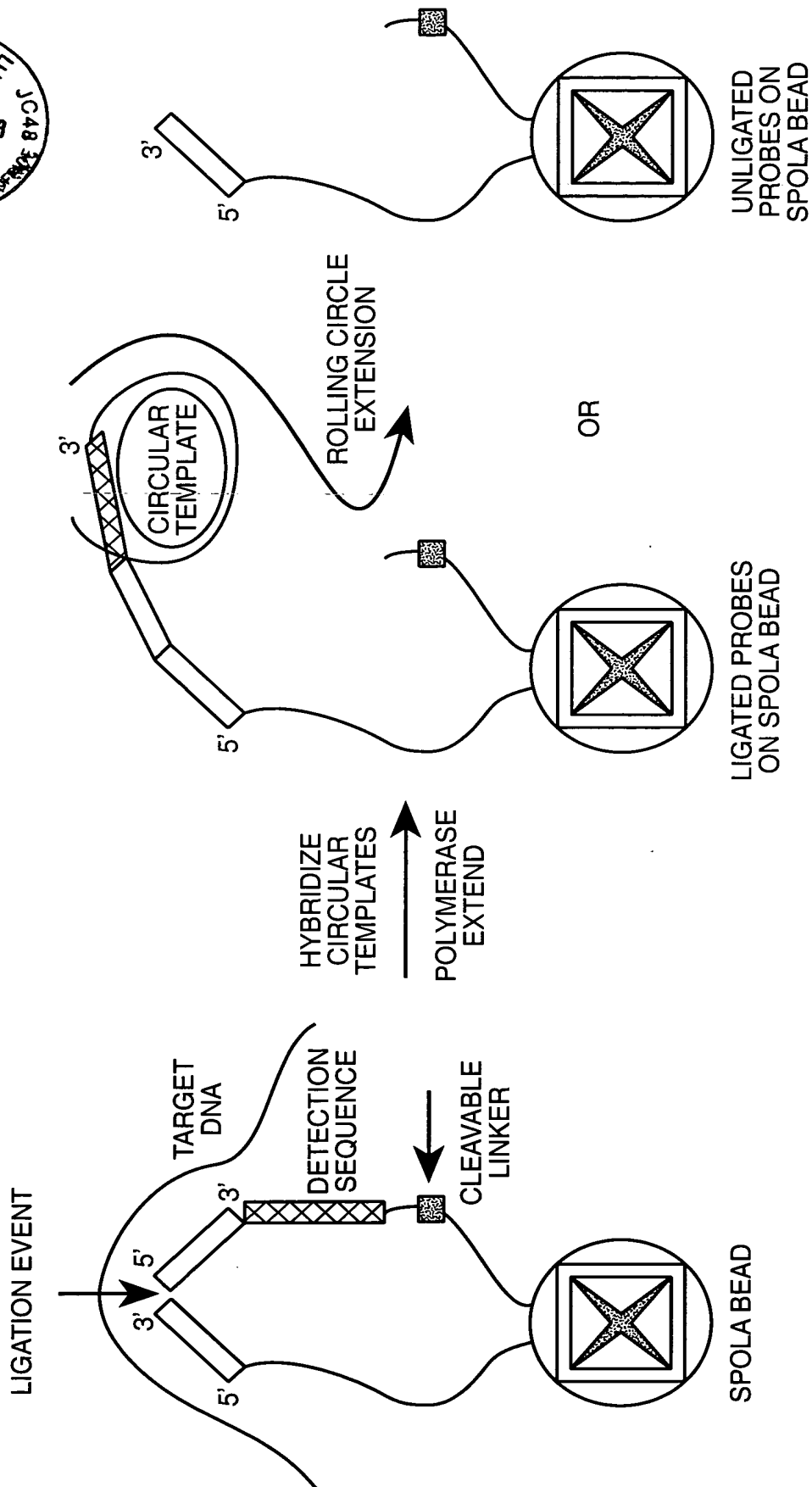
**FIG.\_6B**

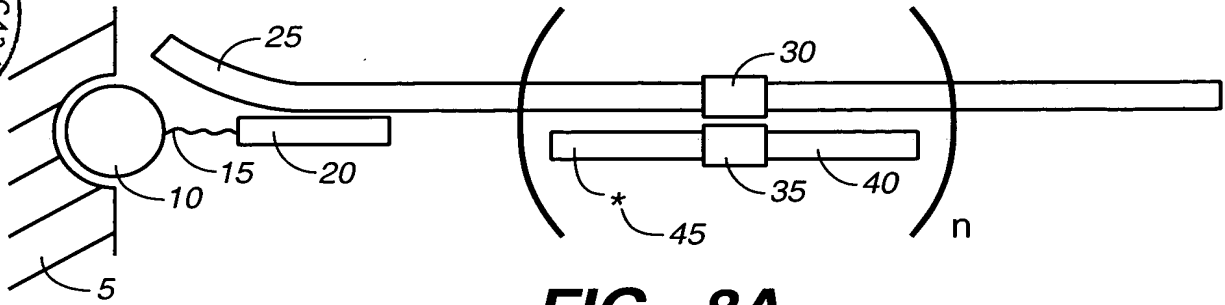


**FIG.\_7A-1**

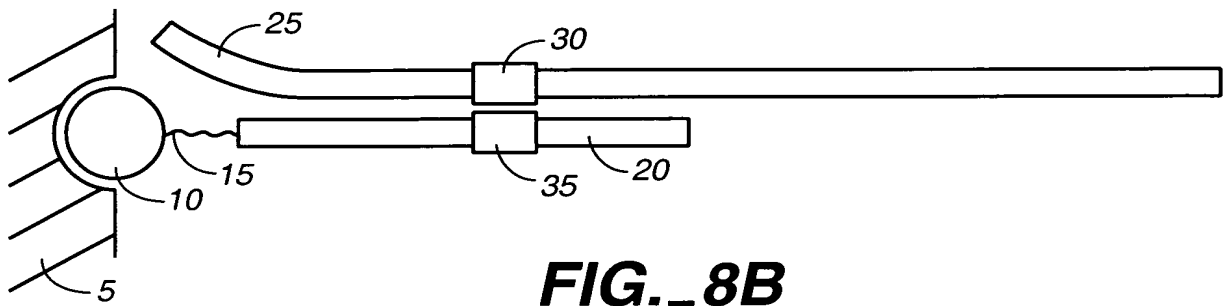
**FIG. 7A-2**

**FIG. 7B****FIG. 7D**

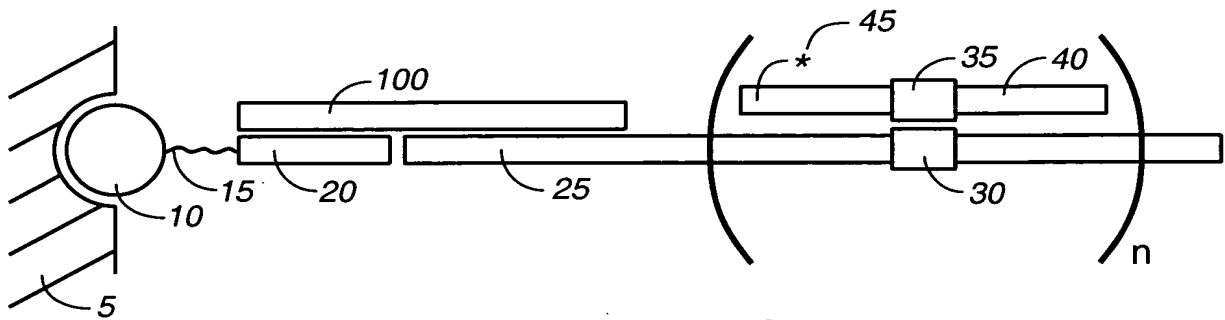
**FIG. 7C**



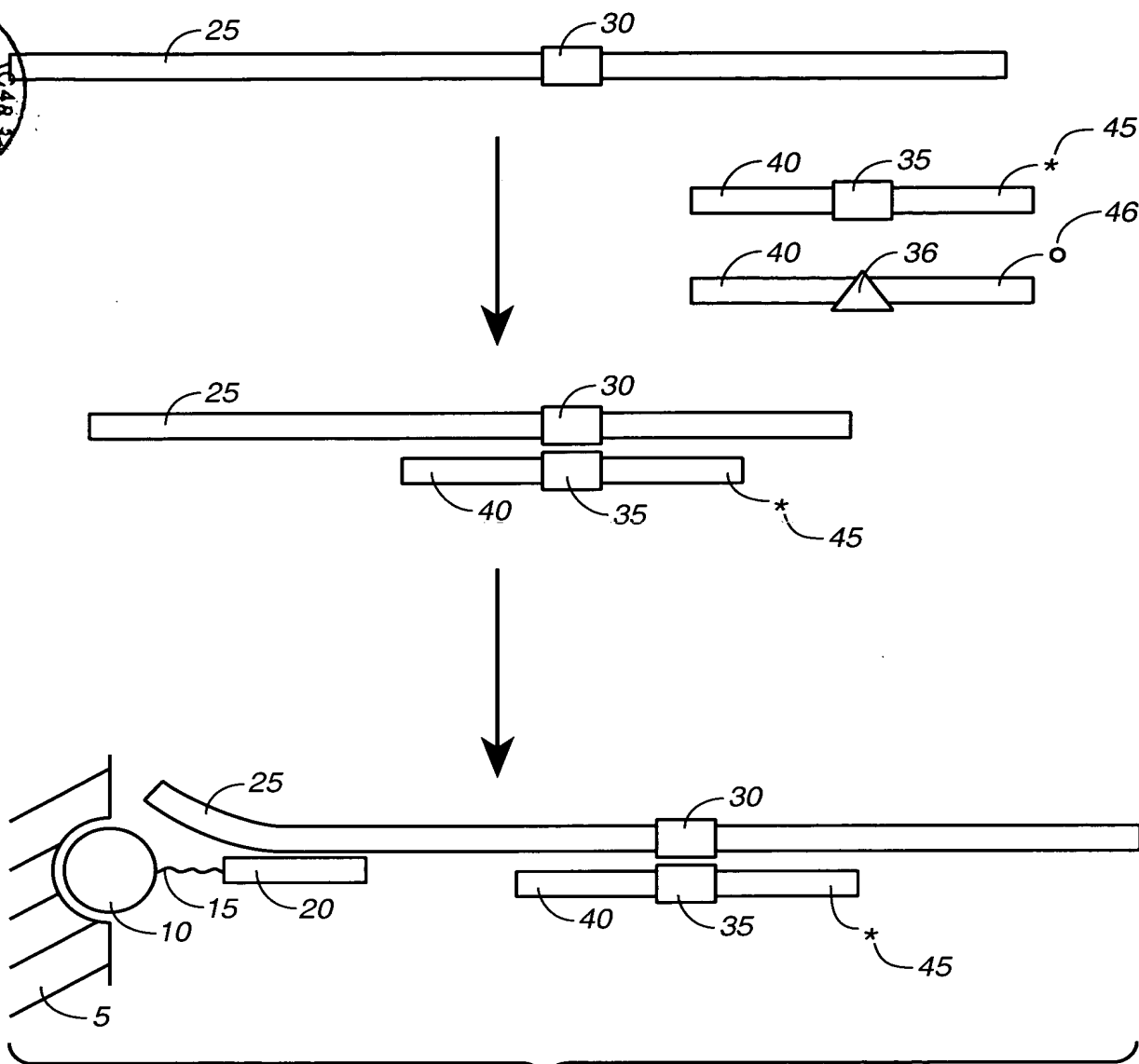
**FIG. 8A**



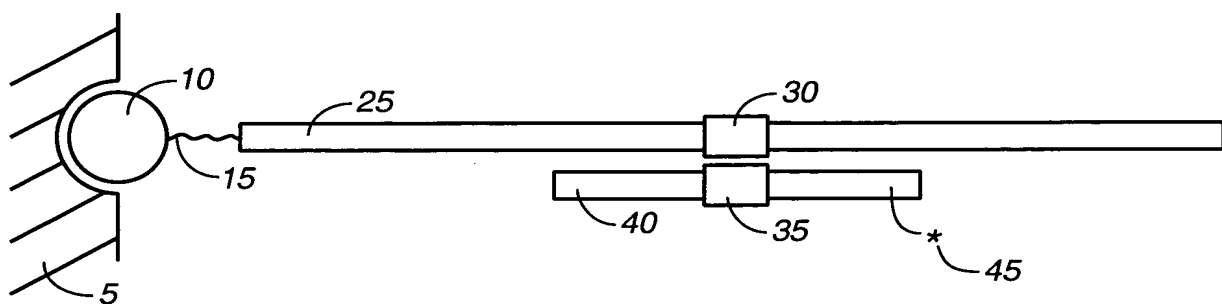
**FIG. 8B**



**FIG. 8C**

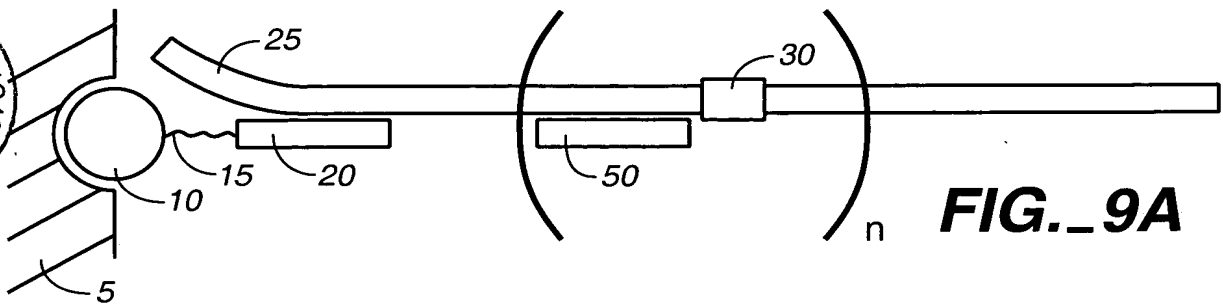
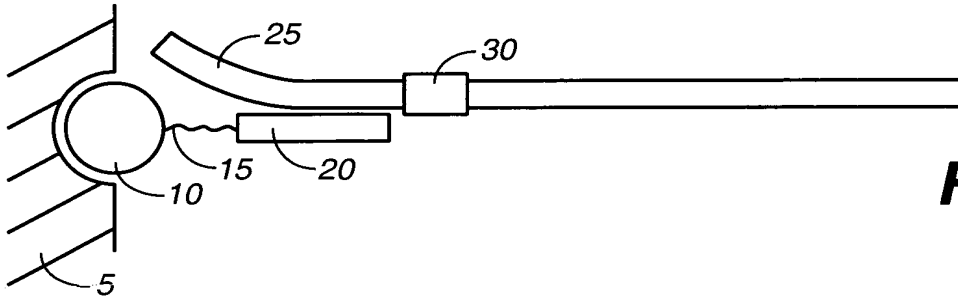
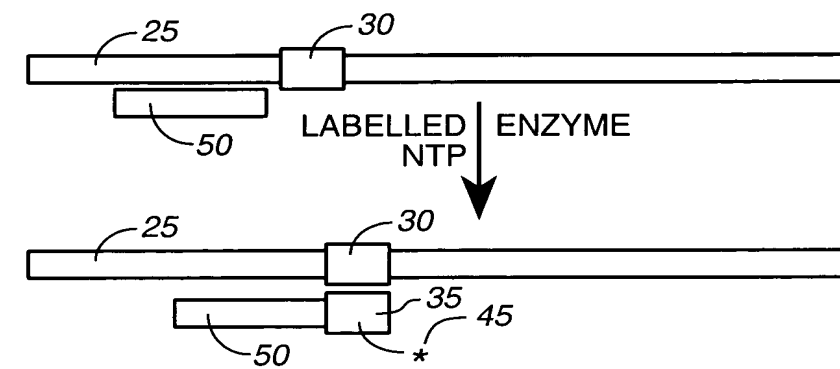


**FIG. 8D**



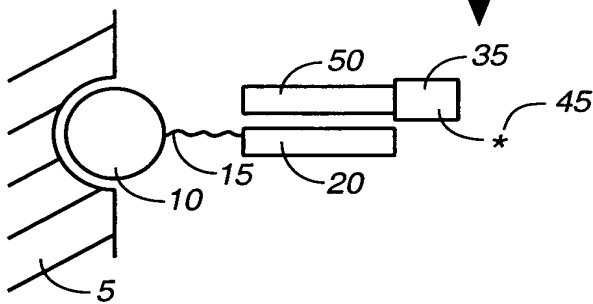
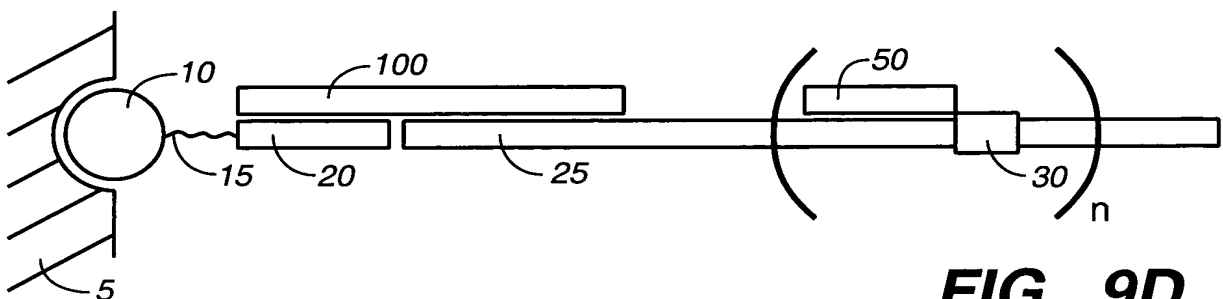
**FIG. 8E**

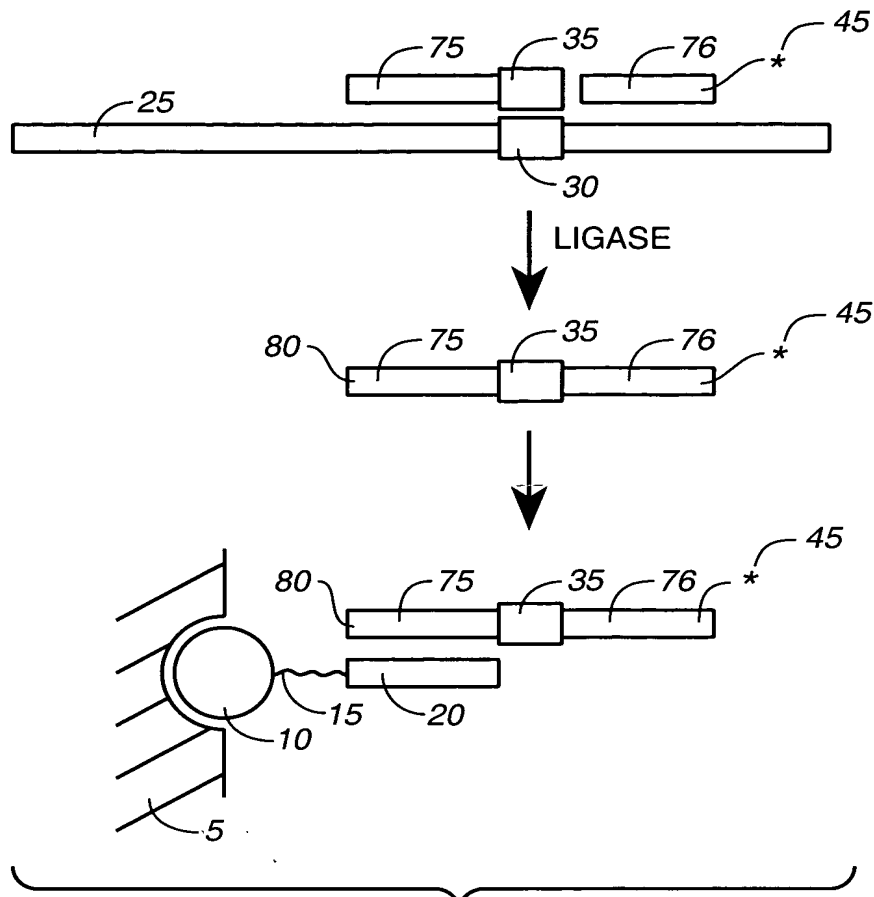
14 / 36

**FIG. 9A****FIG. 9B**

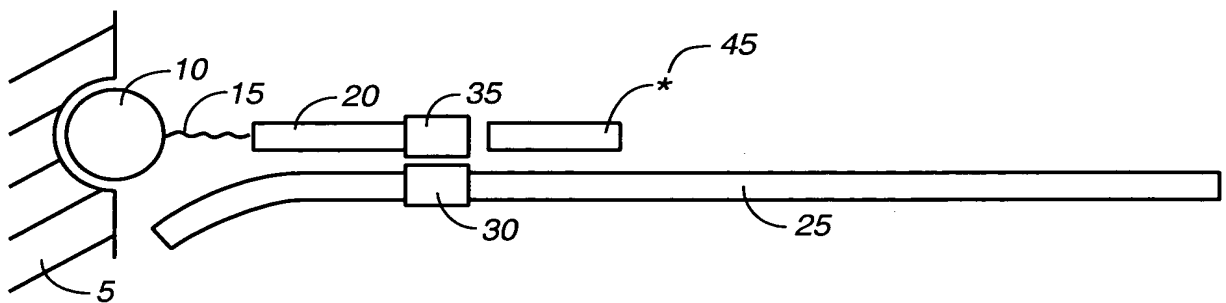
OPTIONAL REMOVAL OF  
UNEXTENDED PRIMERS

DENATURE,  
ADD TO ARRAY

**FIG. 9C****FIG. 9D**

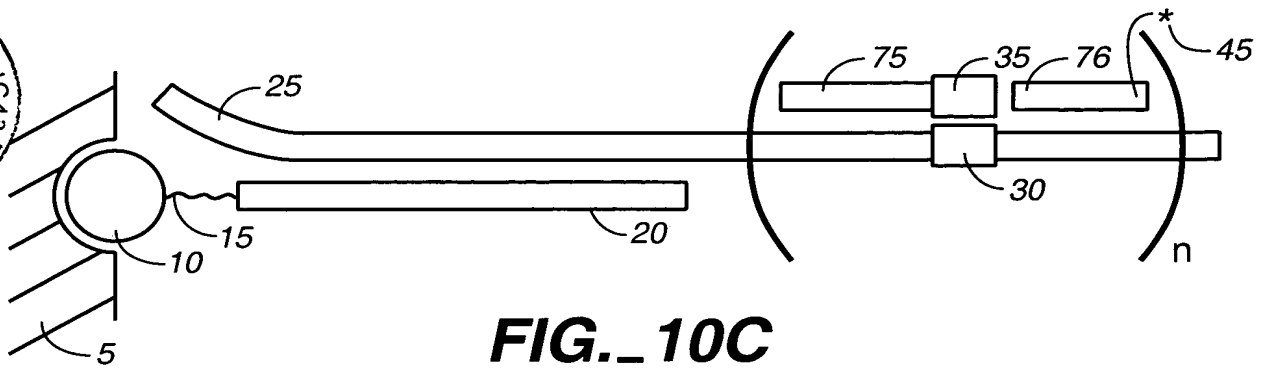
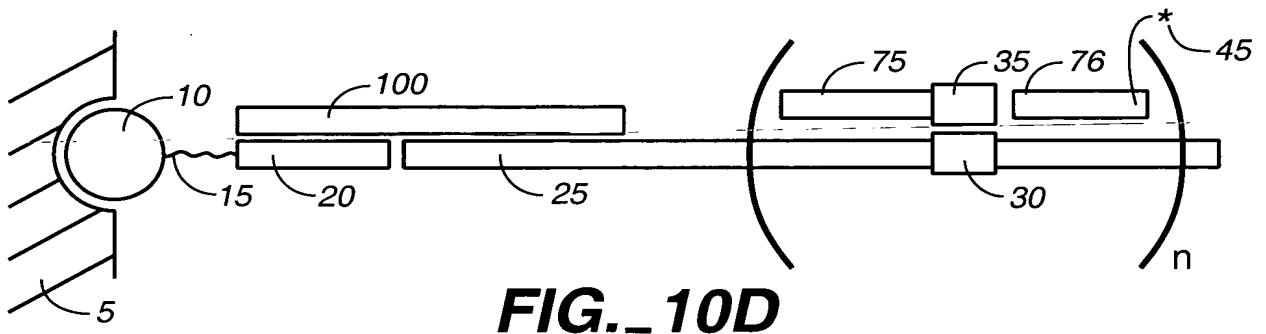
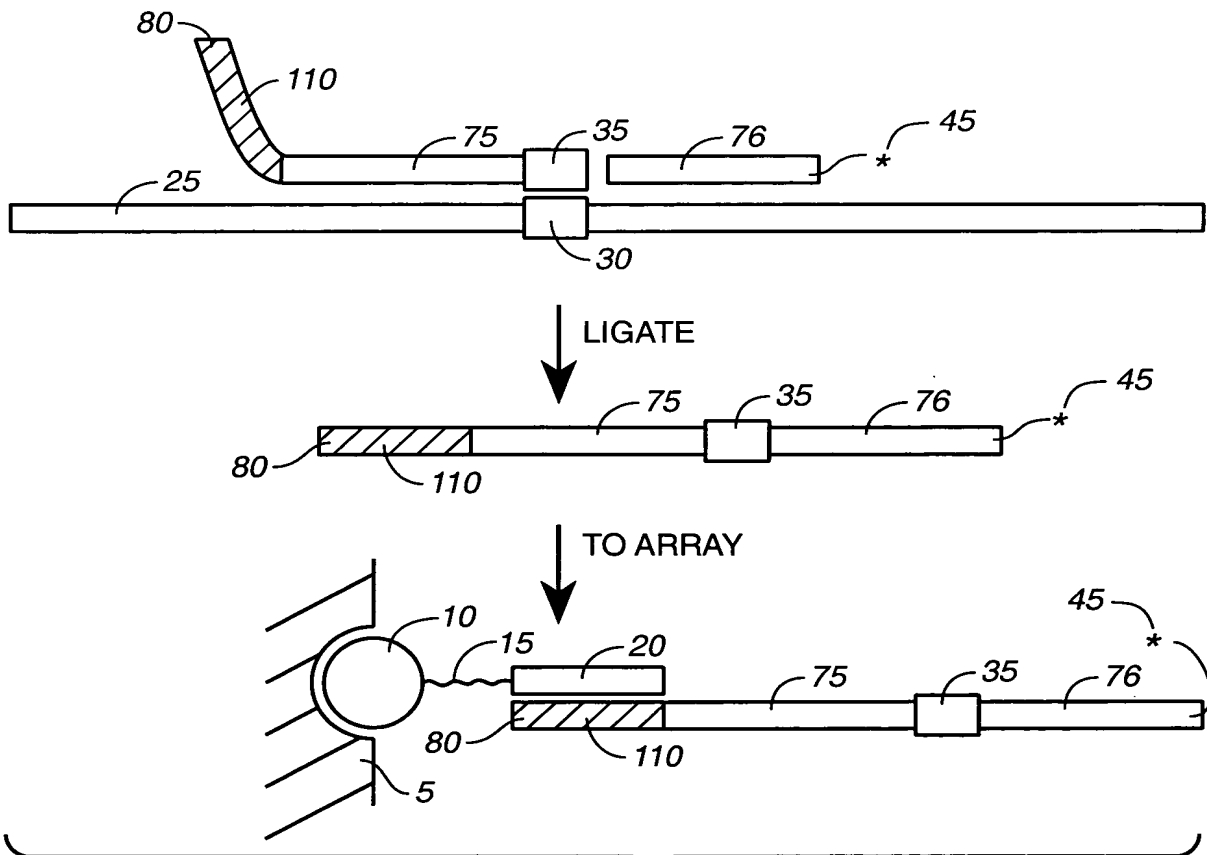


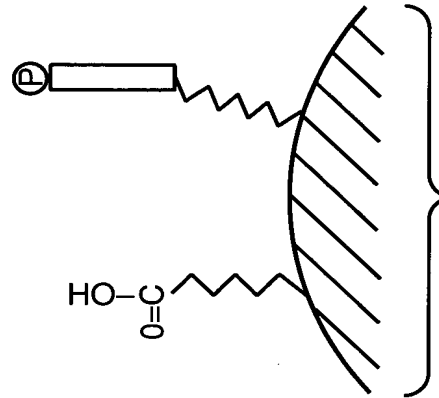
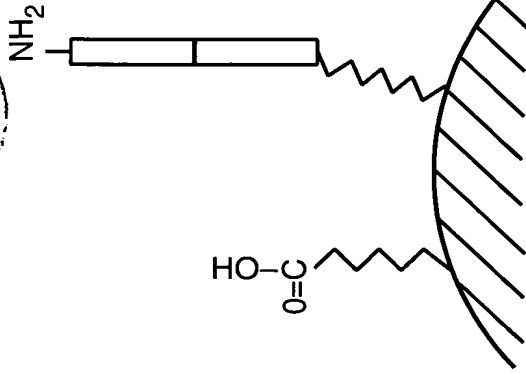
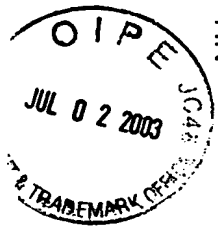
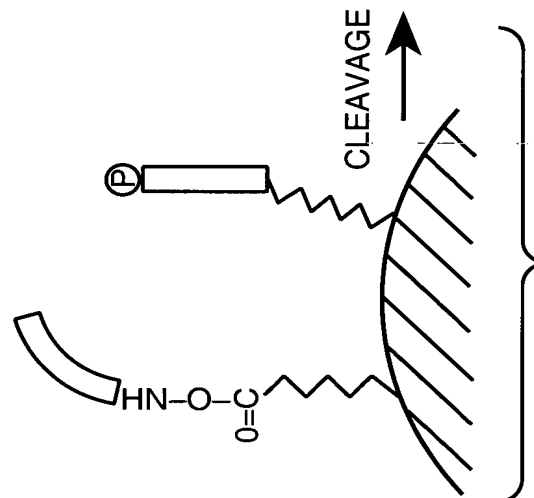
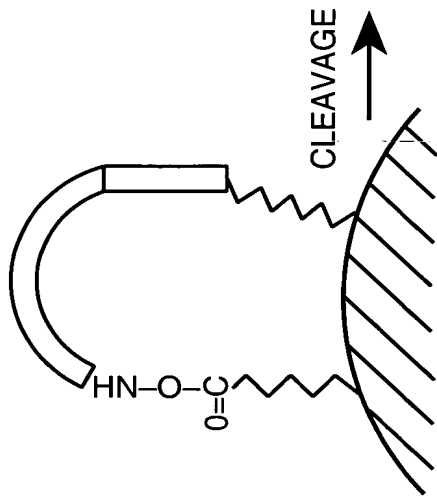
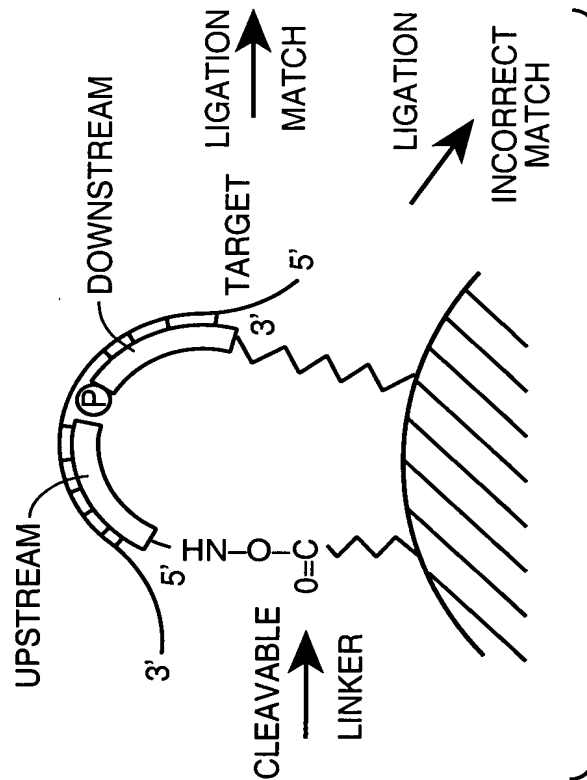
**FIG. 10A**

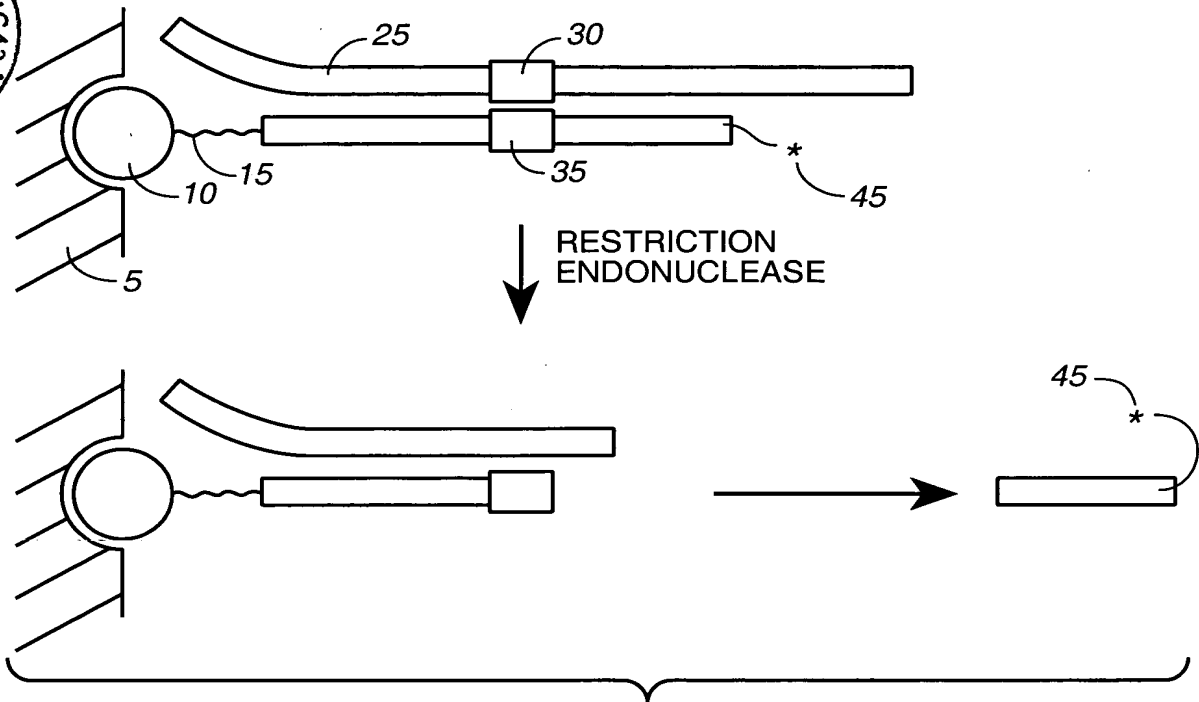
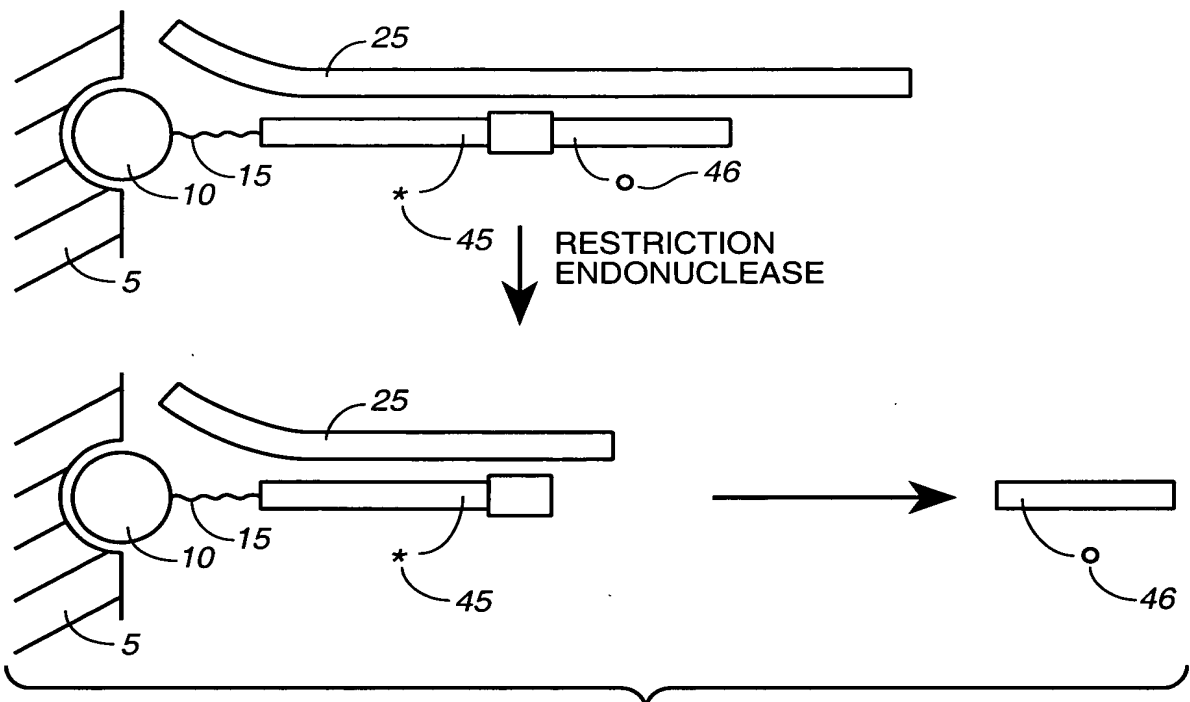


**FIG. 10B**

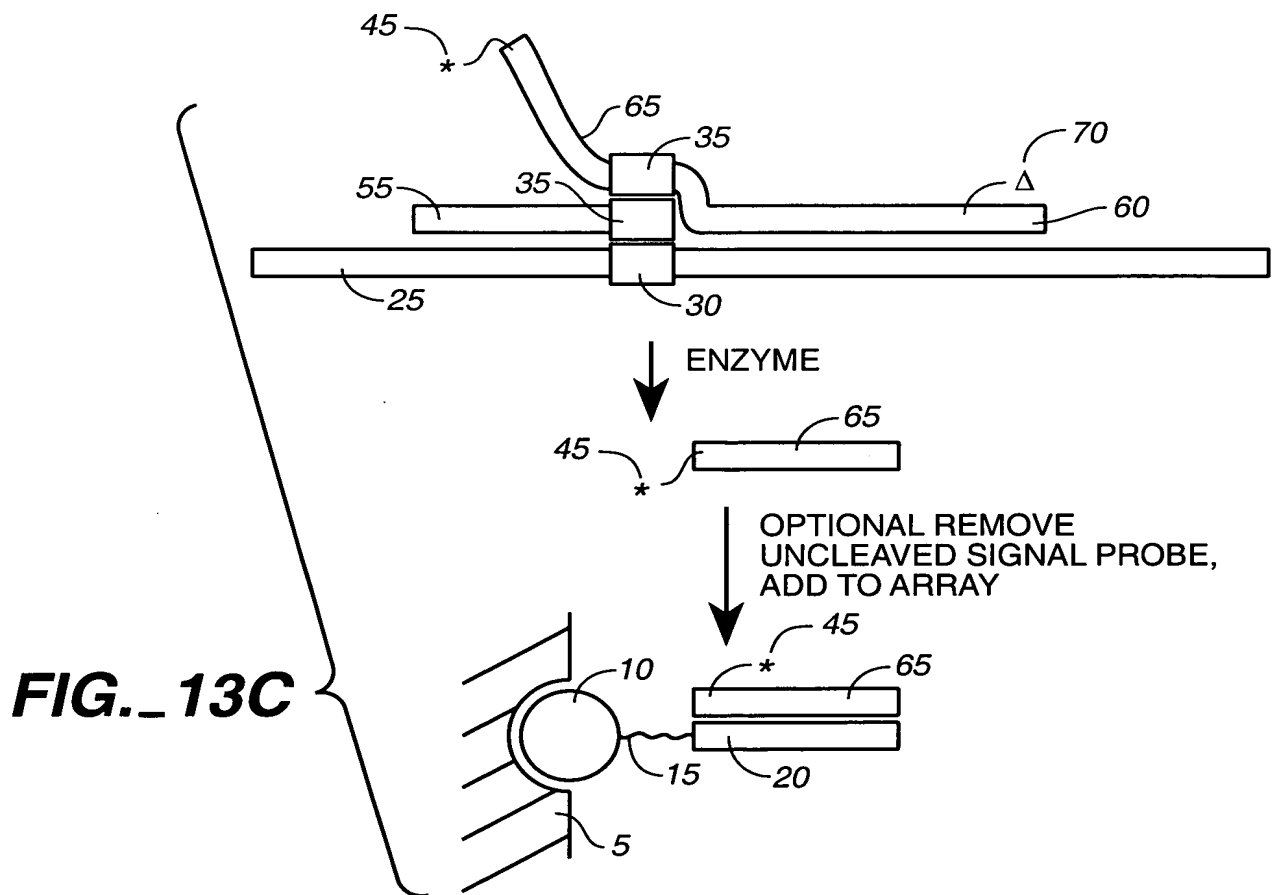
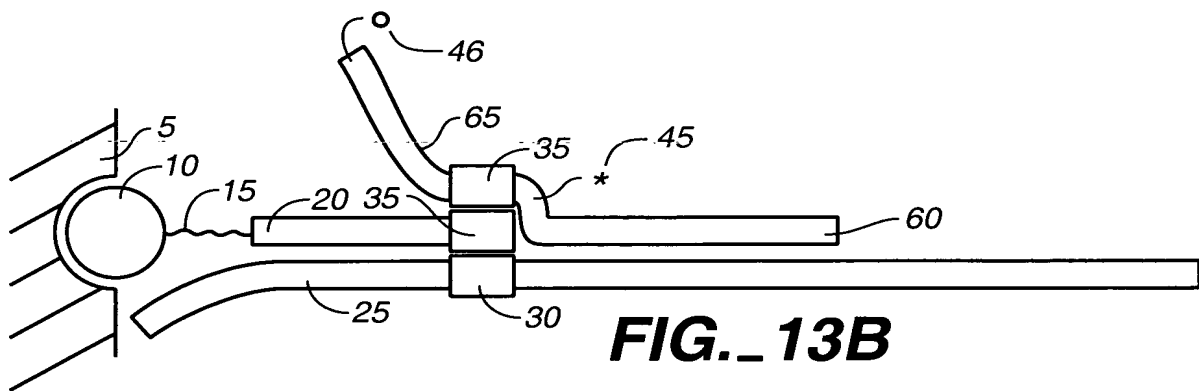
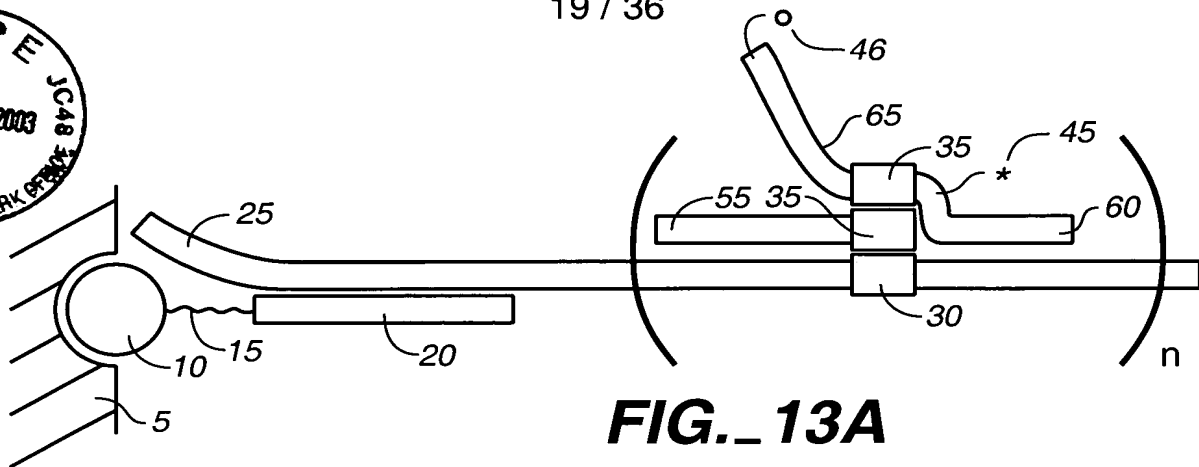


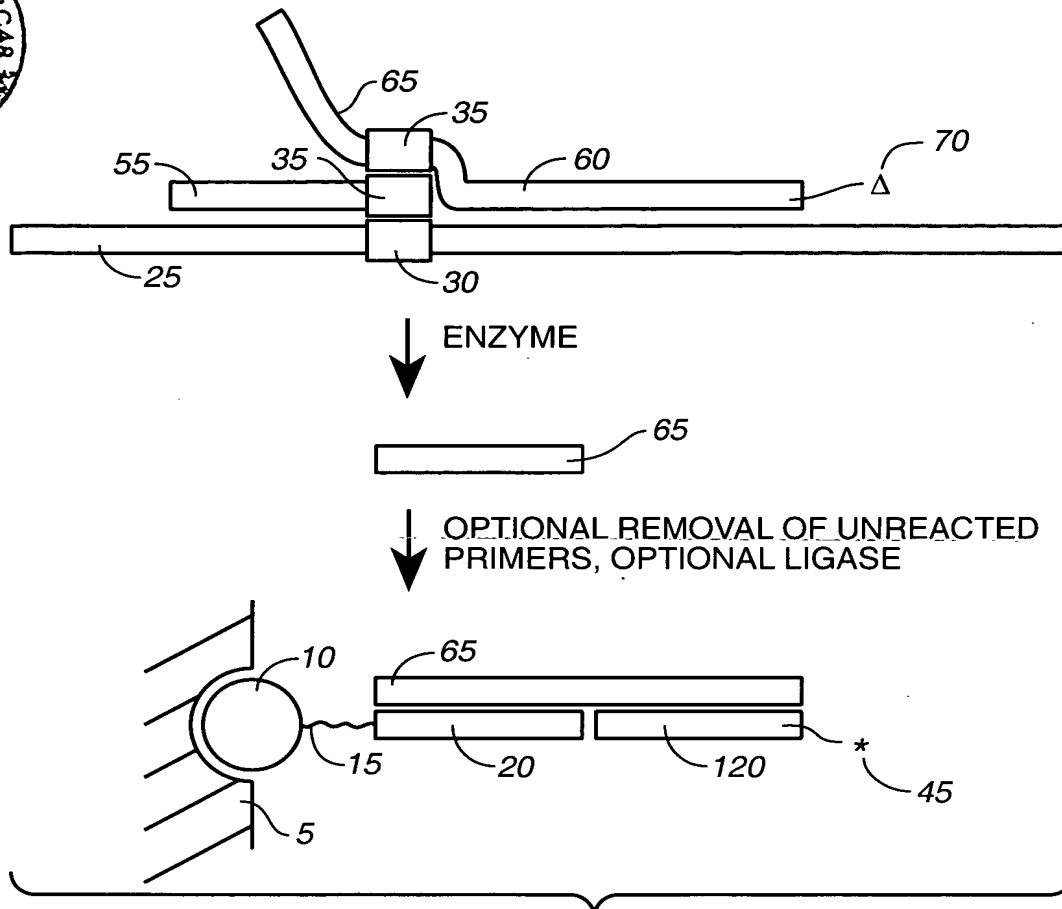
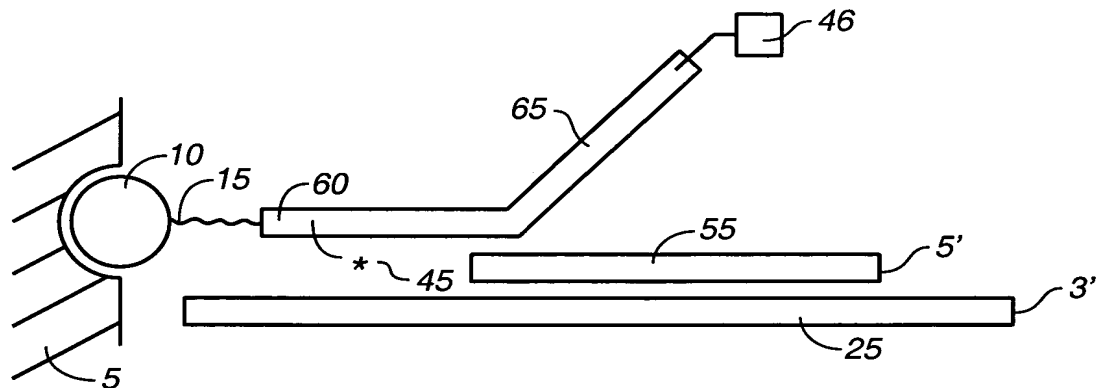
**FIG. 10C****FIG. 10D****FIG. 10E**

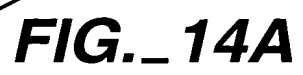
**FIG.\_11C****FIG.\_11B****FIG.\_11A**

**FIG. 12A****FIG. 12B**

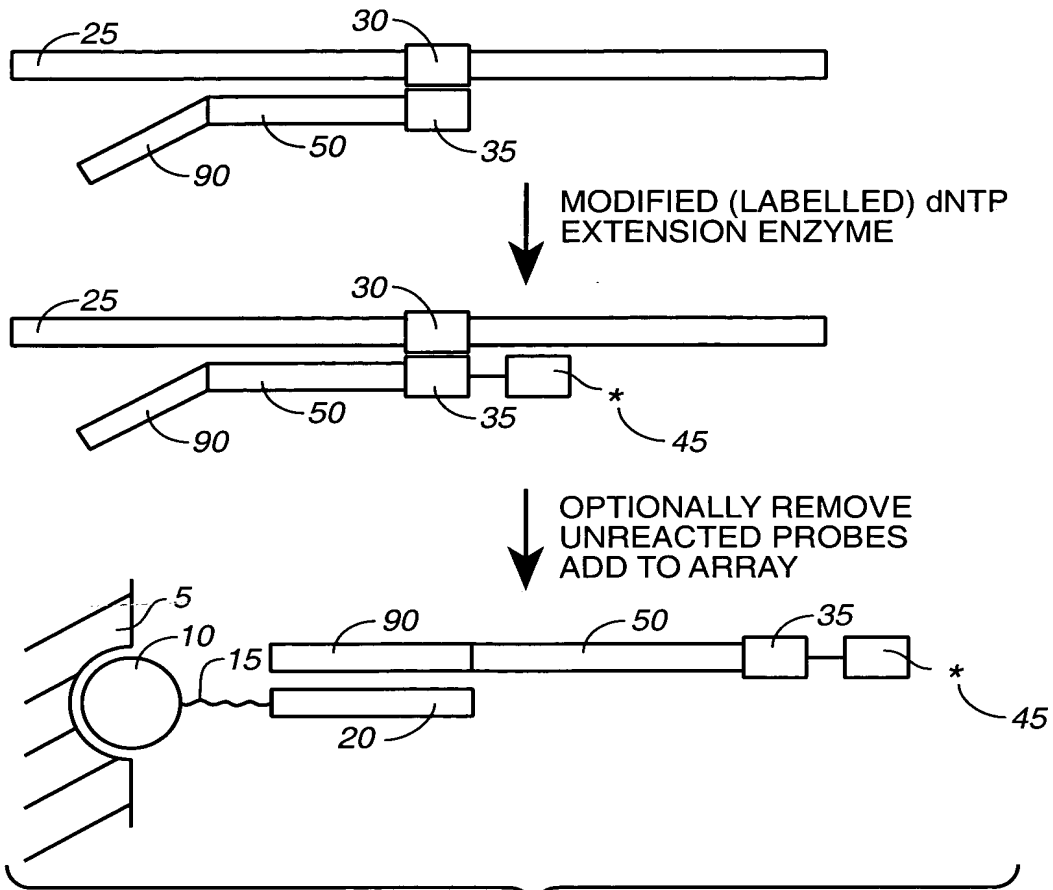
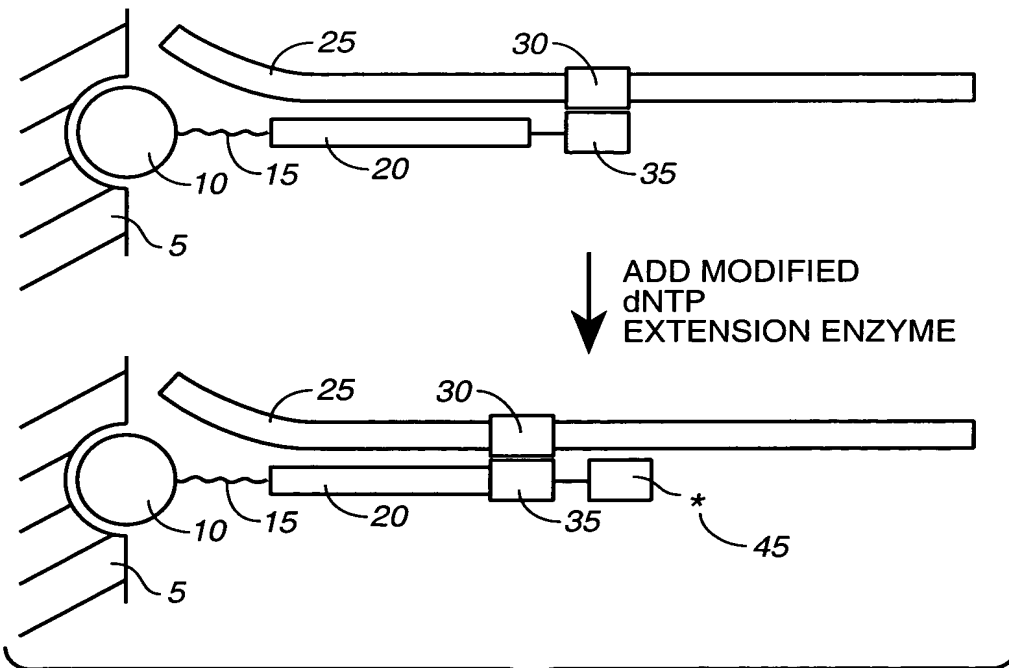
19 / 36



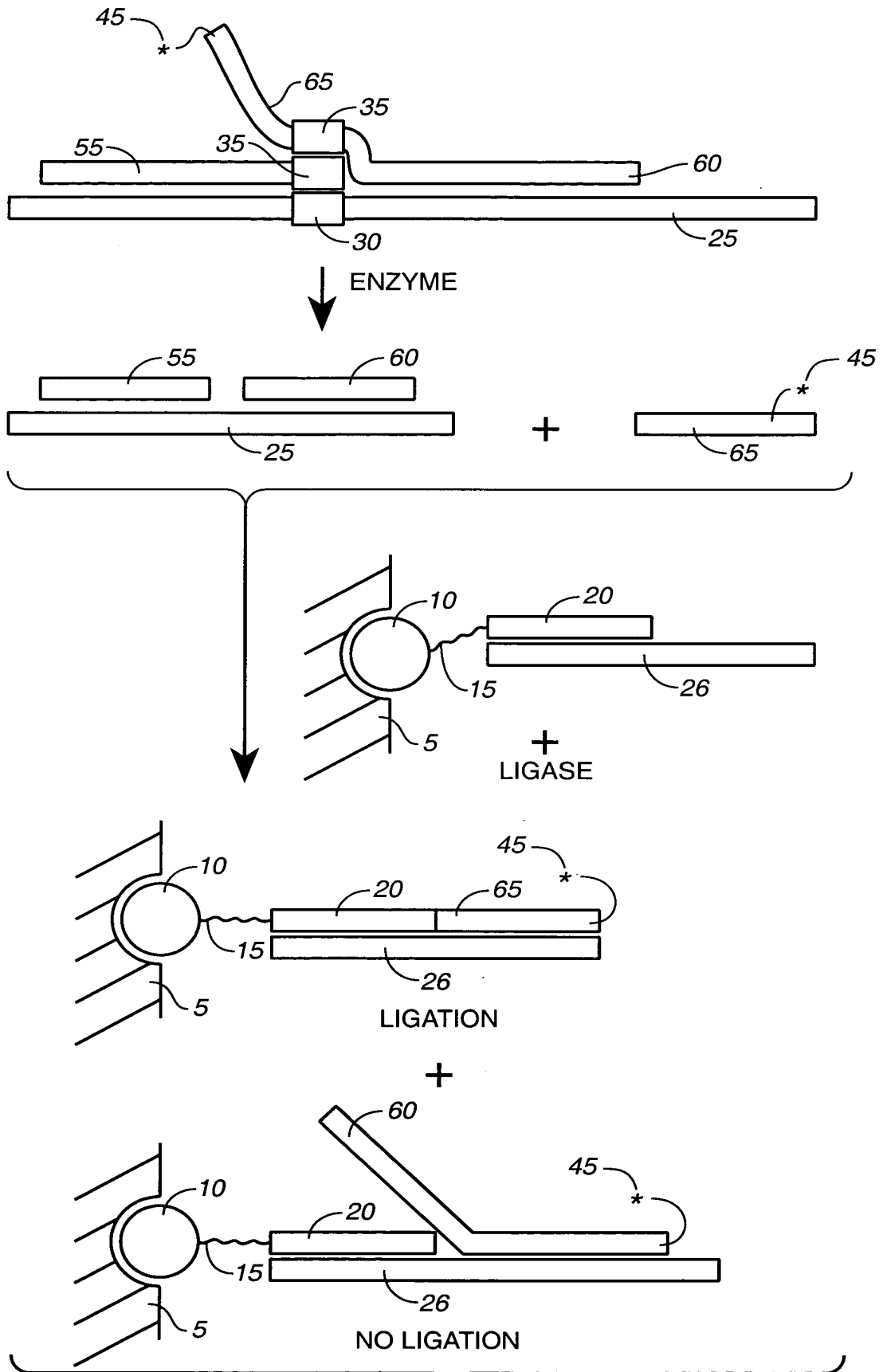
**FIG.\_13D****FIG.\_13E**



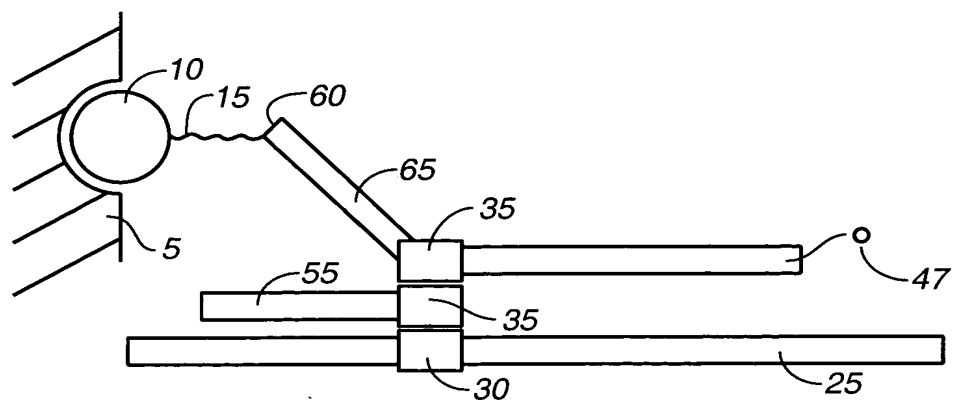
22 / 36

**FIG.\_14C****FIG.\_14D**

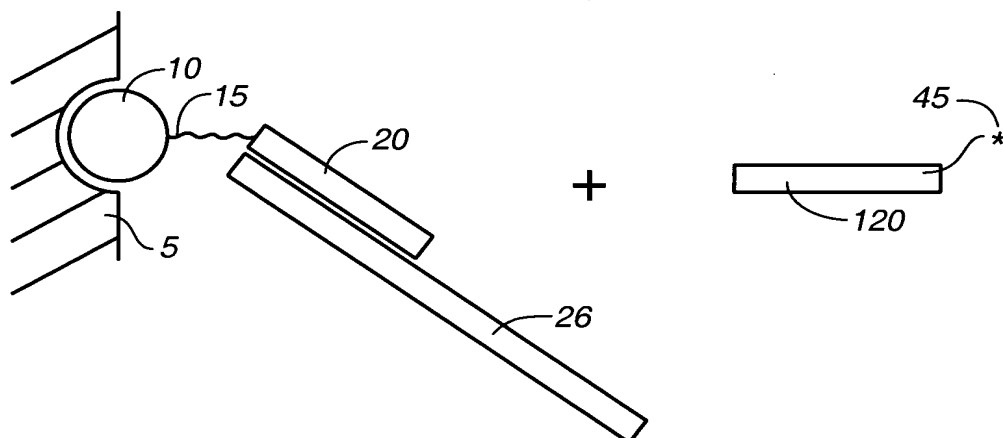
23 / 36

**FIG. 15A**

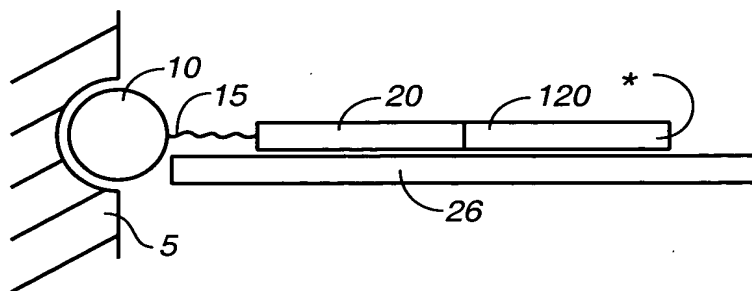




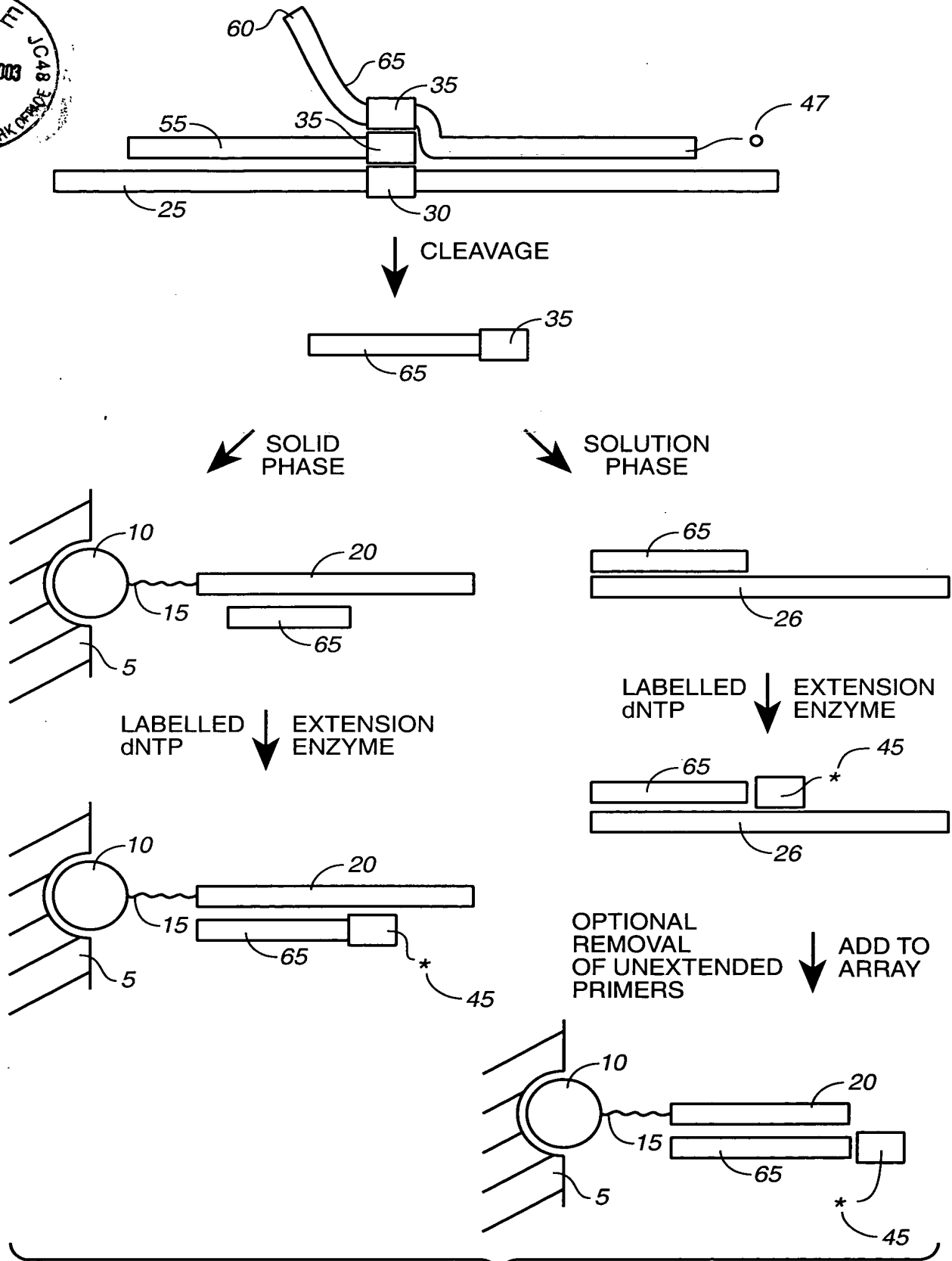
CLEAVAGE ENZYME  
TARGET TEMPLATE



LIGATION

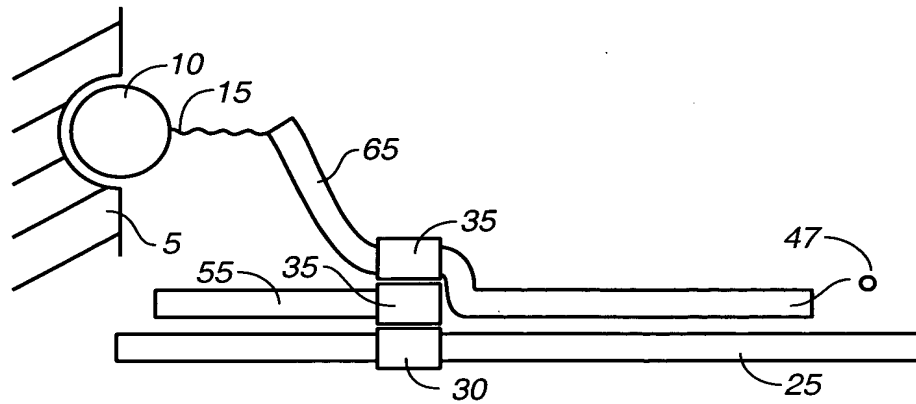


**FIG. 15B**

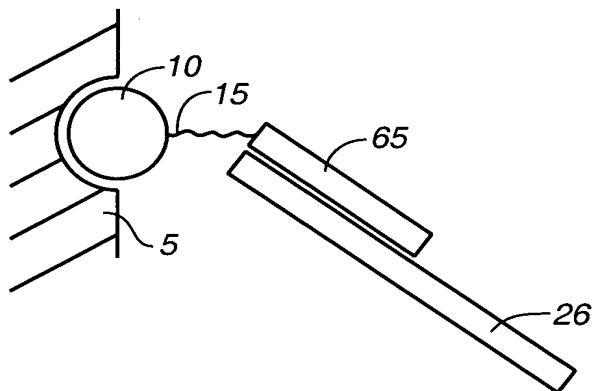


**FIG. 16A**

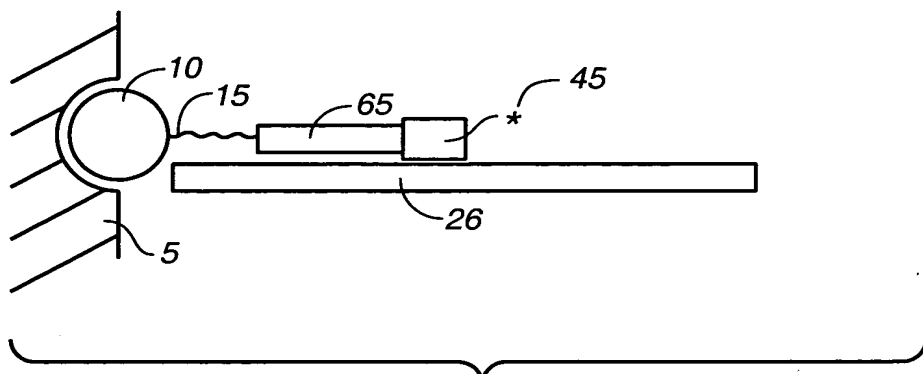
+



CLEAVAGE  
ADD TARGET TEMPLATE

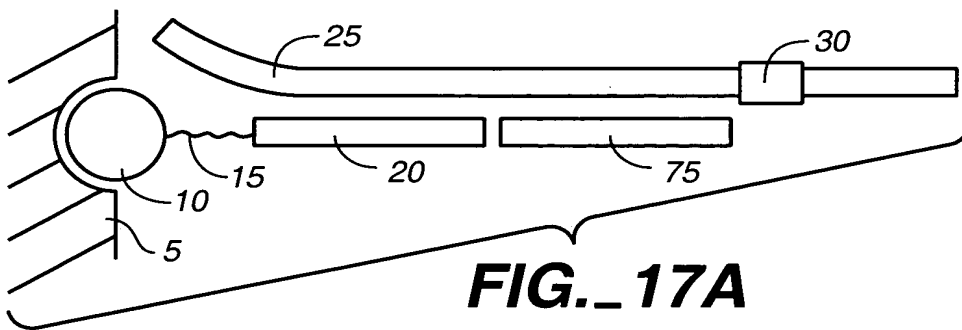
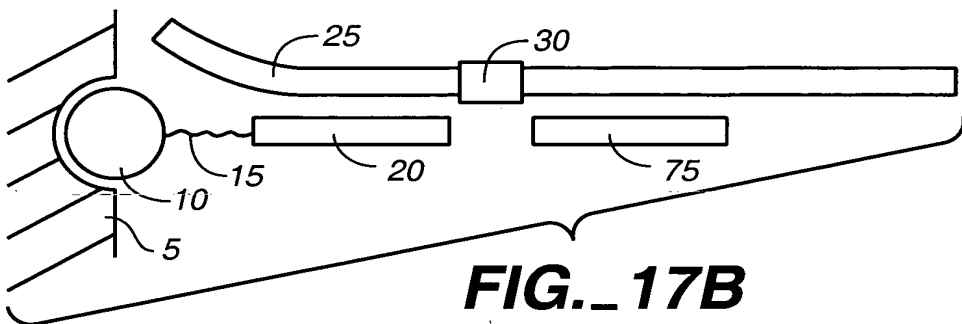
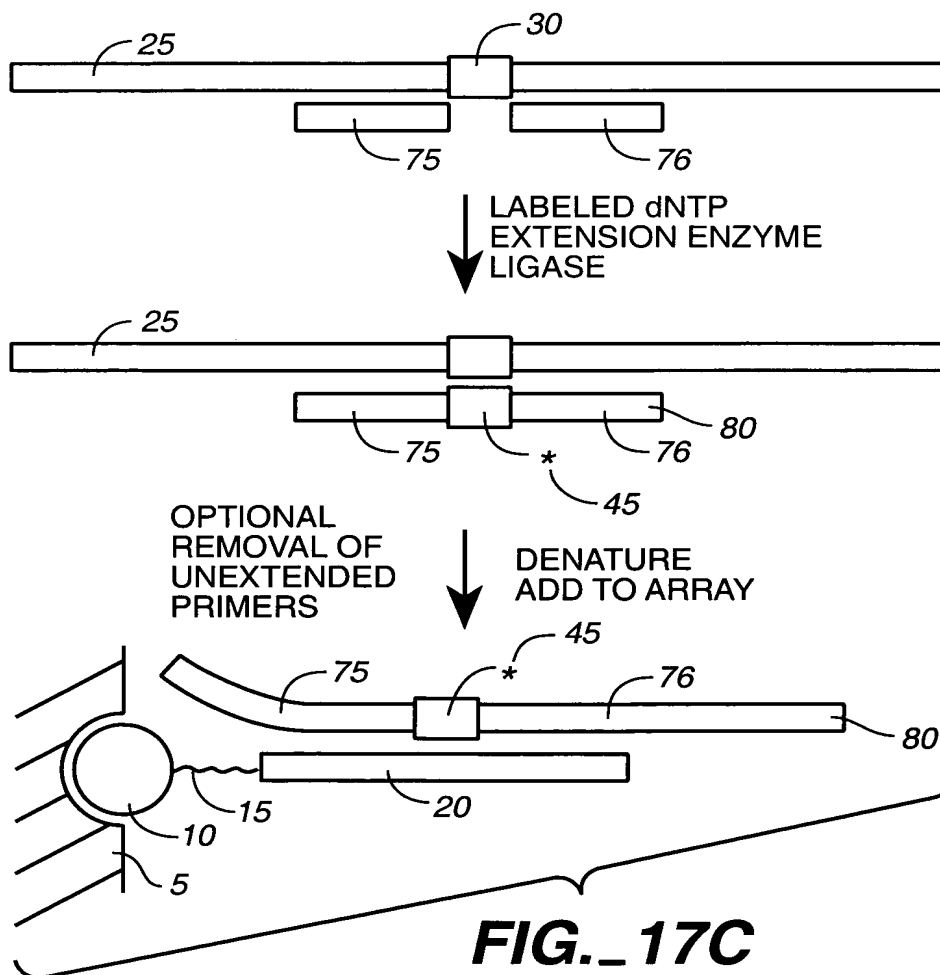


LABELLED  
dNTP EXTENSION  
ENZYME



**FIG. 16B**

27 / 37

**FIG. 17A****FIG. 17B**



3' CCC ————— TTTTTTTT-P5'   
 cDNA

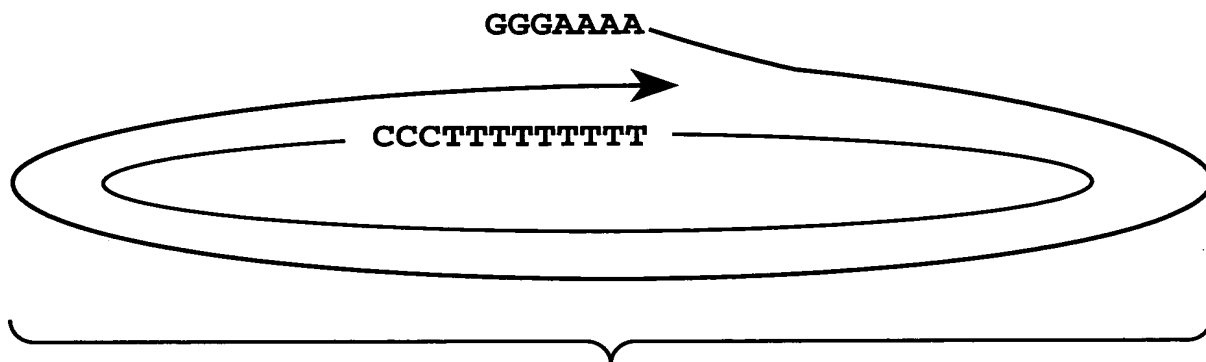
(1) CIRCULARIZE cDNA  
WITH GUIDE LINKER

GGGAAA  
CCCTTTTTTTT  
P

(2) LIGATE

GGGAAA  
CCCTTTTTTTT

(3) EXTEND AS  
ROLLING CIRCLE



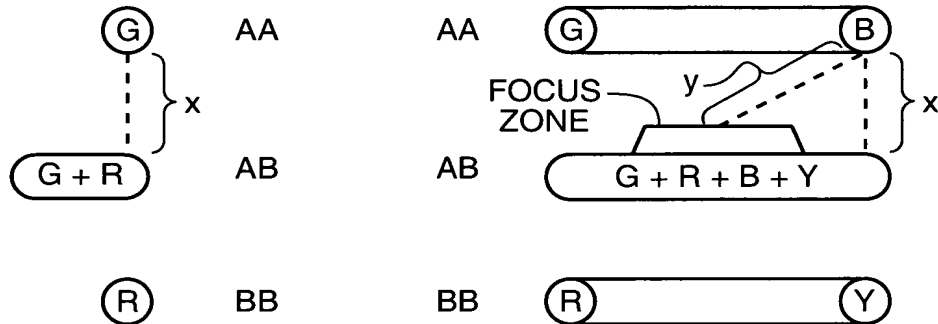
**FIG. 18**

SINGLE LABELED PROBE

GENOTYPE	SIGNAL
AA	G / G
AB	G / R
BB	R / R

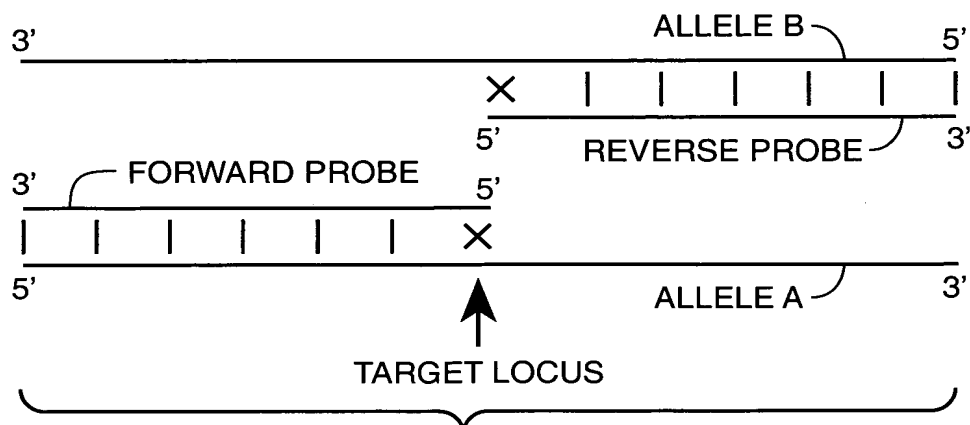
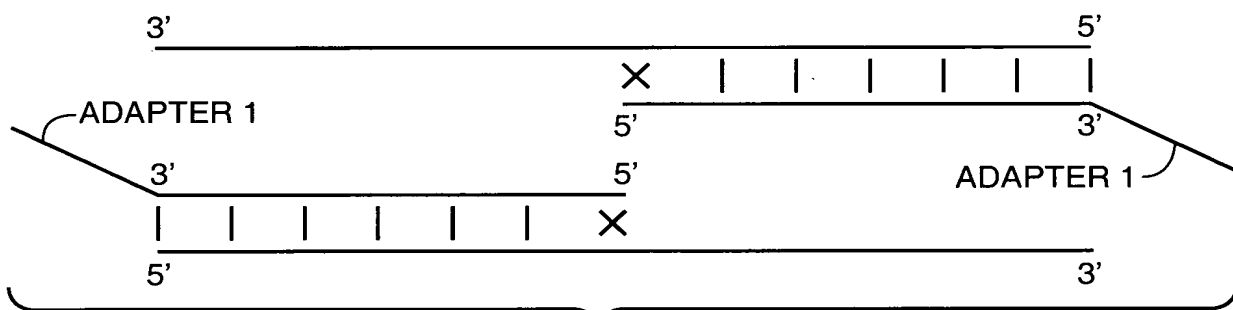
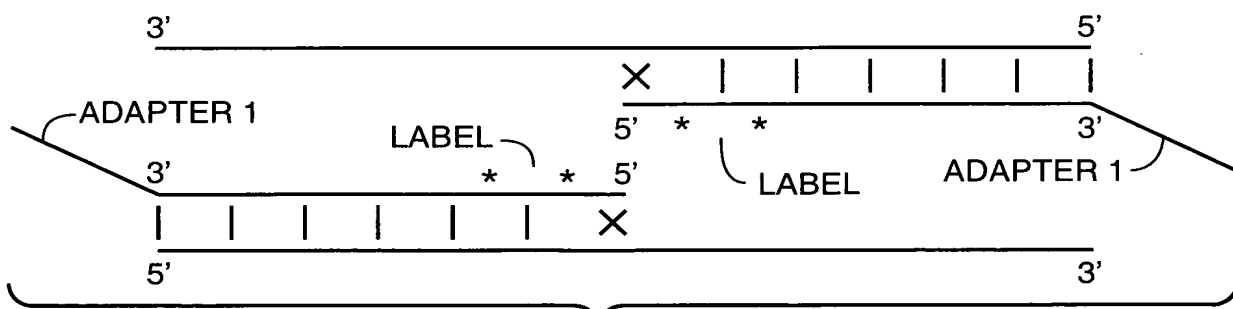
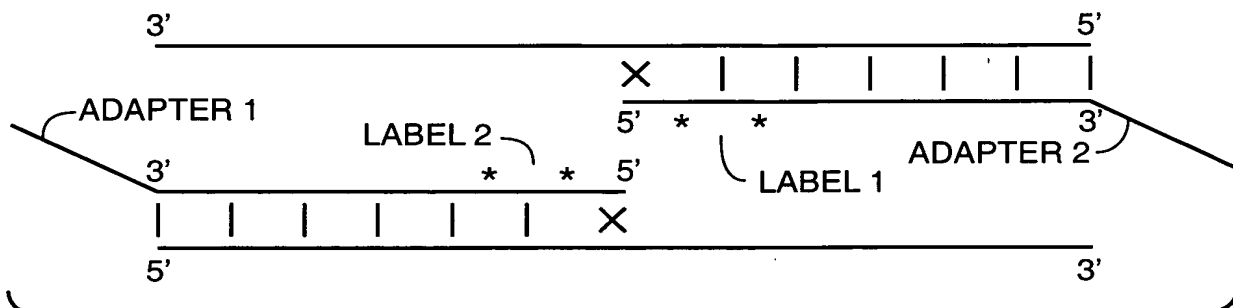
MULTI-LABELED PROBE

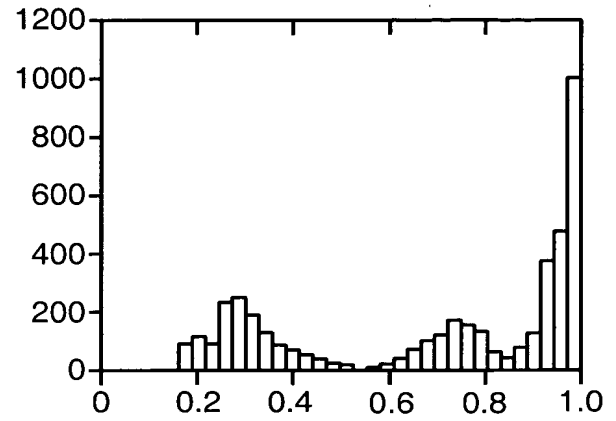
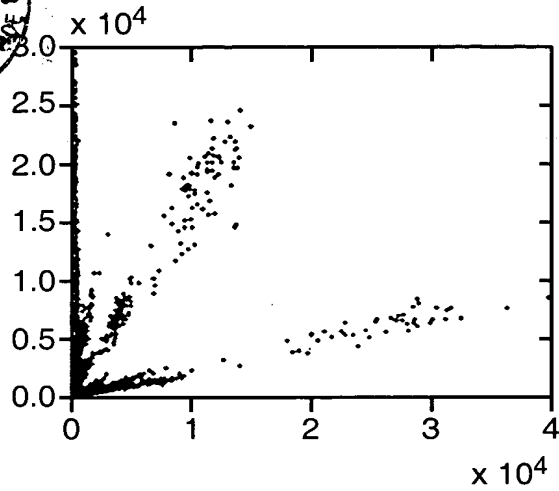
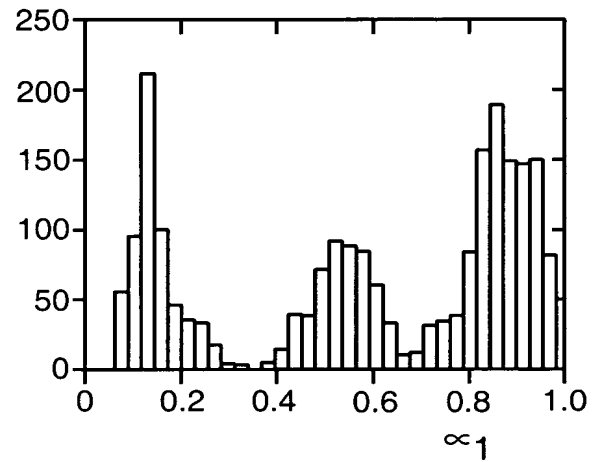
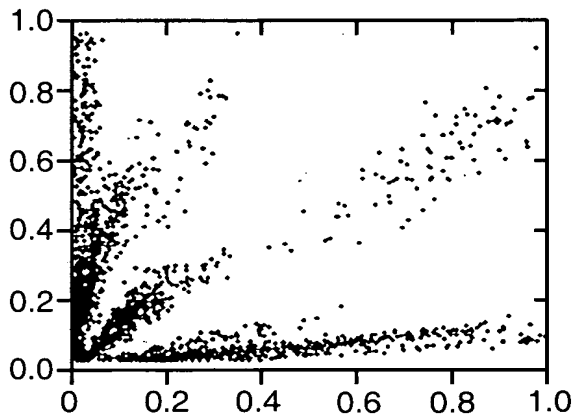
GENOTYPE	SIGNAL
AA	G,B / G,B
AB	G,B / R,Y
BB	R,Y / R,Y

SIGNAL RANGE

x = SINGLE LABEL DISTANCE  
y = MULTI-LABEL DISTANCE

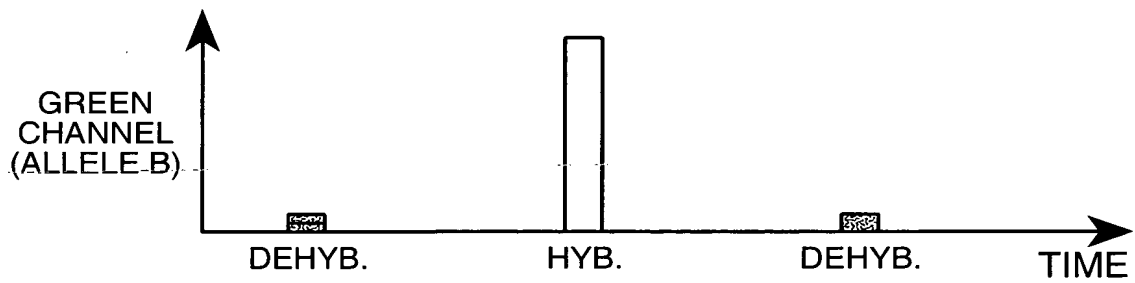
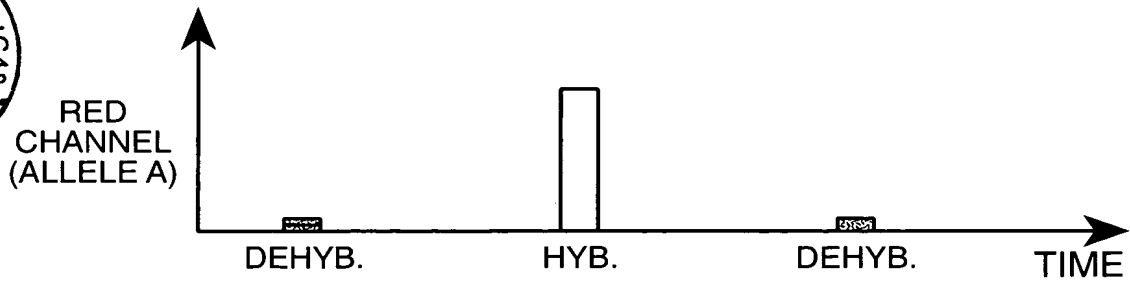
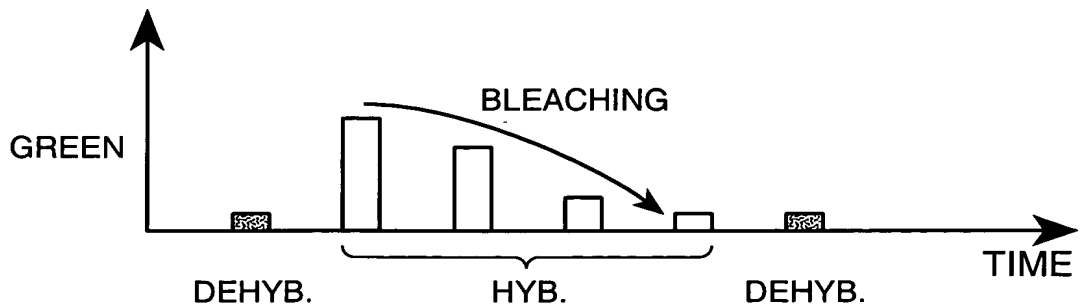
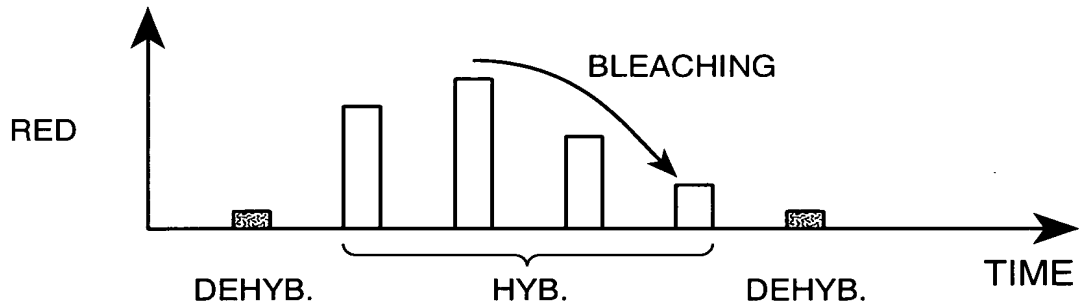
**FIG. 19**

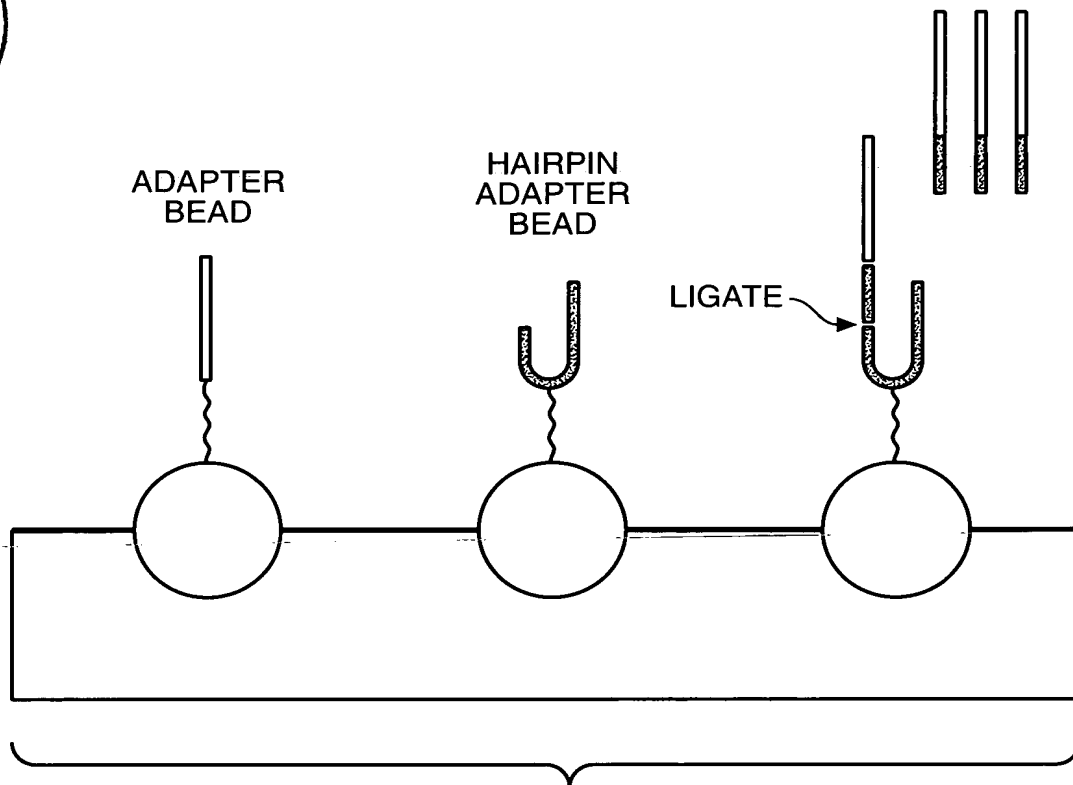
**FIG.\_20A****FIG.\_20B****FIG.\_20C****FIG.\_20D**

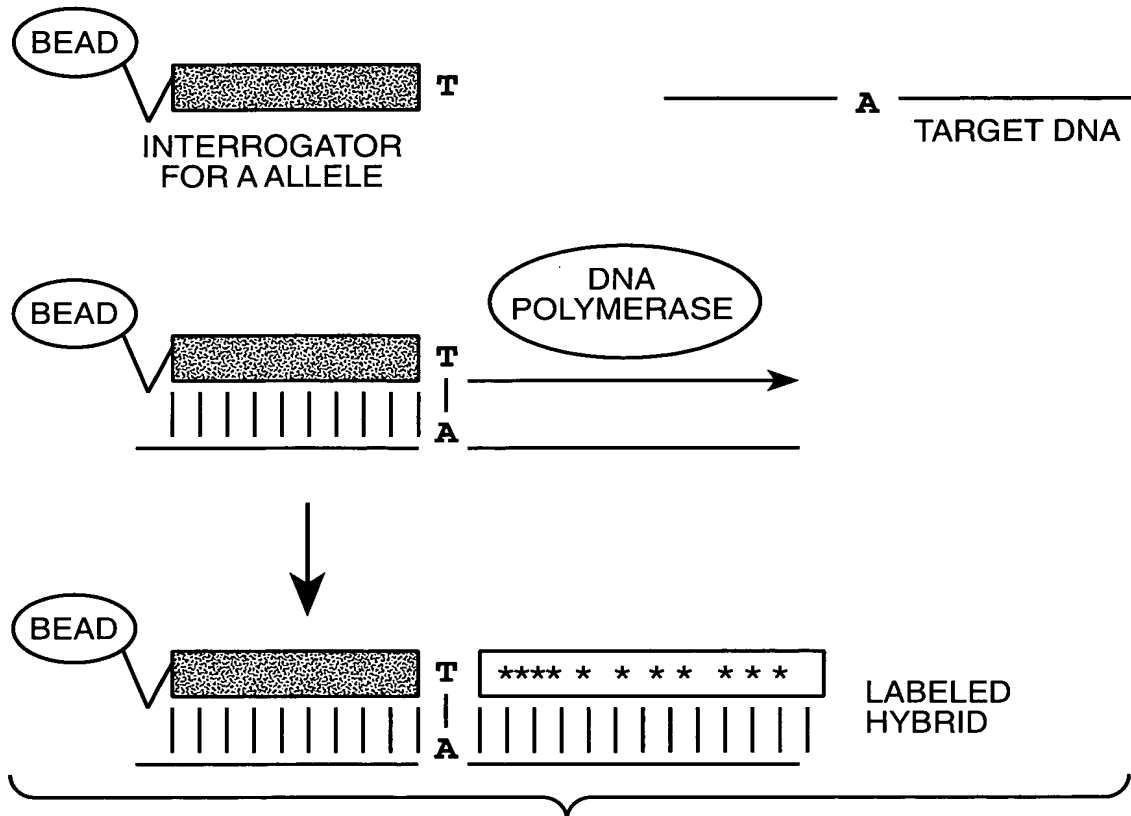
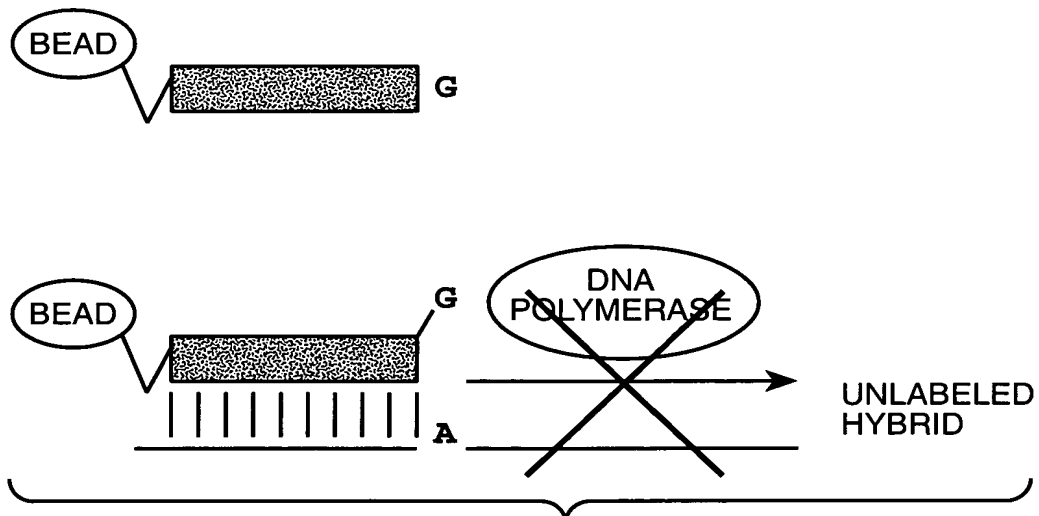
**BEFORE NORMALIZATION****AFTER NORMALIZATION****FIG. 21**

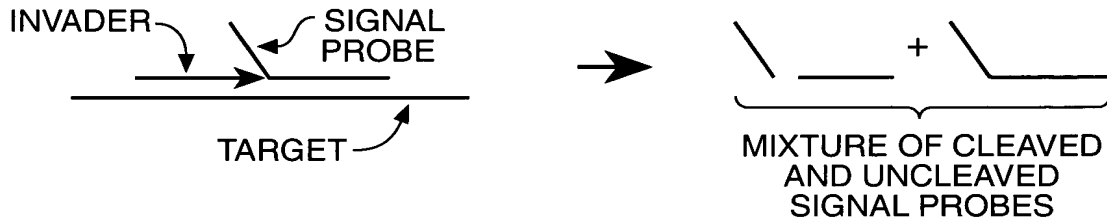
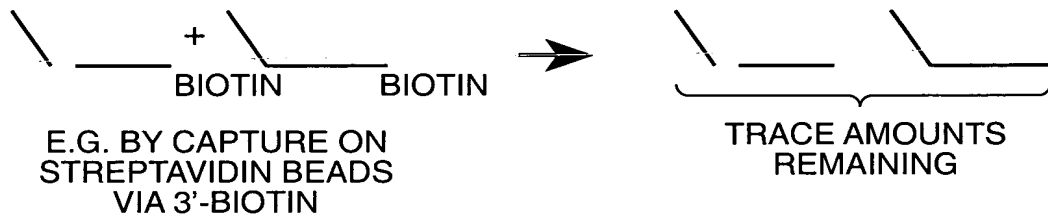
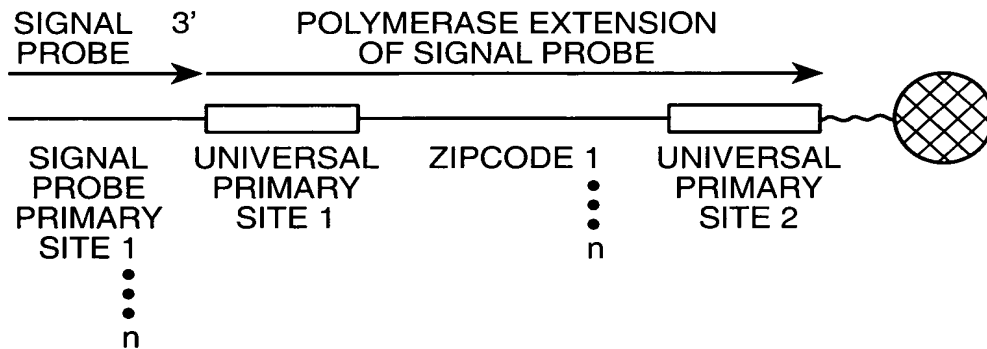


32 / 36

**FIG. 22A****FIG. 22B**

**FIG.\_23**

**MATCH TO SNP ALLELE****FIG.\_24A****MISMATCH TO SNP ALLELE****FIG.\_24B**

**INVADER - PCR****1) INVADER REACTION****2) REMOVAL OF UNCLEAVED SIGNAL PROBES****3) SIGNAL PROBE PRIMES SYNTHESIS OF AMPLICON TARGET STRAND****4) PCR AMPLIFICATION**

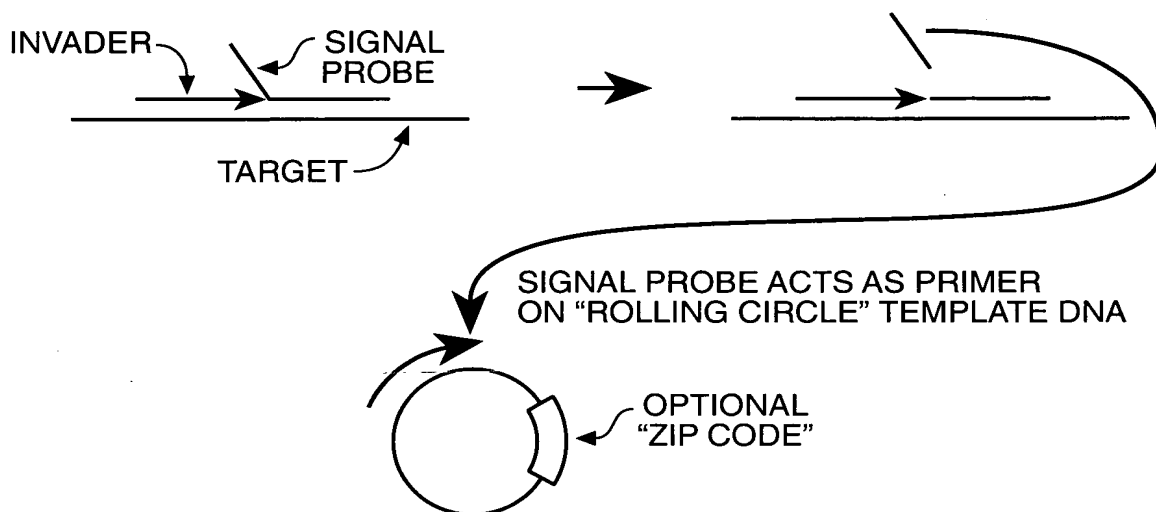
NEWLY SYNTHESIZED TARGET STRANDS ARE DENATURED FROM TEMPLATE AND TRANSFERRED TO PCR REACTION (UNIVERSAL PRIMERS, dNT's, TAQ POLYMERASE) FOR MULTIPLEX PCR. UNIVERSAL PRIMERS ARE LABELLED E.G. WITH BIOTIN.

**5) ARRAY HYBRIDIZATION - PCR AMPLICONS CONTAINING ZIPCODES ARE HYBRIDIZED TO ARRAY.****FIG.\_25**

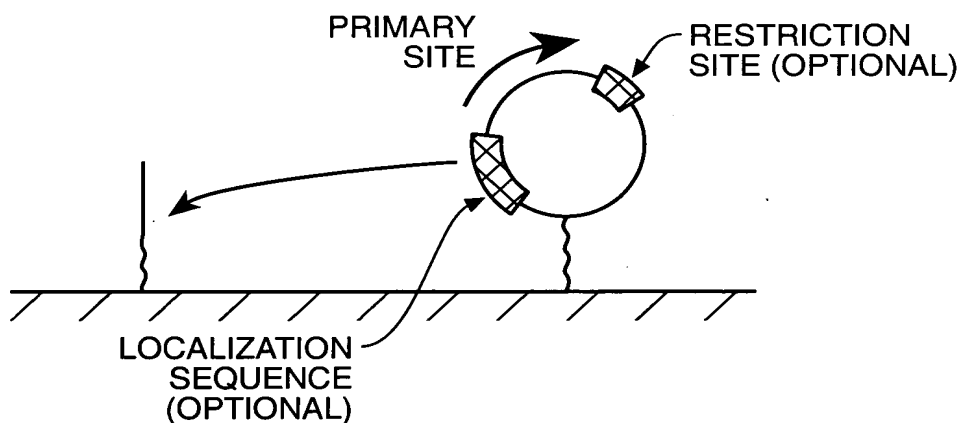


# INVADER - ROLLING CIRCLE

## 1) INVADER REACTION



## SOLID PHASE VERSION:



ROLLING CIRCLE TEMPLATE IS TETHERED TO SURFACE E.G. TO LOCALIZED "FEATURES" IN ARRAY FORMAT, OR TO BEADS.

ROLLING CIRCLE PRODUCTS CAN BE LOCALIZED E.G. BY HYBRIDIZATION TO ADJACENT PROBES OR RECOVERED IN LIQUID PHASE FOR HYBRIDIZATION TO A DETECTION ARRAY, E.G. BY ENZYMATIC CLEAVAGE.

**FIG. 26**